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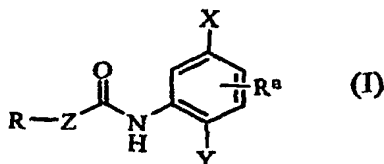
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(54) Title: BENZAMIDE DERIVATIVES AS INHIBITORS OF HISTONE DEACETYLASE



(57) Abstract: The invention relates to the inhibition of histone deacetylase. The invention provides compounds which are derivatives of benzamide and suitable in methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions .

## BENZAMIDE DERIVATIVES AS INHIBITORS OF HISTONE DEACETYLASE

**BACKGROUND OF THE INVENTION**

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 60/744,427, filed April 7, 2006 and U.S. Provisional Application Serial No. 60/886,019, filed January 22, 2007.

**Field of the Invention**

[0002] This invention relates to the inhibition of histone deacetylase. More particularly, the invention relates to compounds and methods for inhibiting histone deacetylase enzymatic activity.

**Summary of the Related Art**

[0003] In eukaryotic cells, nuclear DNA associates with histones to form a compact complex called chromatin. The histones constitute a family of basic proteins which are generally highly conserved across eukaryotic species. The core histones, termed H2A, H2B, H3, and H4, associate to form a protein core. DNA winds around this protein core, with the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA. Approximately 146 base pairs of DNA wrap around a histone core to make up a nucleosome particle, the repeating structural motif of chromatin.

[0004] Csordas, *Biochem. J.*, **286**: 23-38 (1990) teaches that histones are subject to posttranslational acetylation of amino groups of *N*-terminal lysine residues, a reaction that is catalyzed by histone acetyl transferase (HAT1). Acetylation neutralizes the positive charge of the lysine side chain, and is thought to impact chromatin structure. Indeed, Taunton *et al.*, *Science*, **272**: 408-411 (1996), teaches that access of transcription factors to chromatin templates is enhanced by histone hyperacetylation. Taunton *et al.* further teaches that an enrichment in underacetylated histone H4 has been found in transcriptionally silent regions of the genome.

[0005] Histone acetylation is a reversible modification, with deacetylation being catalyzed by a family of enzymes termed histone deacetylases (HDACs). Grozinger *et al.*, *Proc. Natl. Acad. Sci. USA*, **96**: 4868-4873 (1999), teaches that HDACs are divided into two classes, the first represented by yeast Rpd3-like proteins, and the second represented by yeast Hda1-like proteins. Grozinger *et al.* also teaches that the human HDAC1, HDAC2, and HDAC3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC4, HDAC5, and

HDAC6, which are members of the second class of HDACs. Kao *et al.*, *Genes & Dev.*, **14**: 55-66 (2000), discloses HDAC7, a new member of the second class of HDACs. More recently, Hu *et al.* *J. Bio. Chem.* **275**:15254-13264 (2000) and Van den Wyngaert, *FEBS*, **478**: 77-83 (2000) disclose HDAC8, a new member of the first class of HDACs. Histone deacetylases HDAC9 – 11 have also been described.

[0006] Richon *et al.*, *Proc. Natl. Acad. Sci. USA*, **95**: 3003-3007 (1998), discloses that HDAC activity is inhibited by trichostatin A (TSA), a natural product isolated from *Streptomyces hygroscopicus*, and by a synthetic compound, suberoylanilide hydroxamic acid (SAHA).

Yoshida and Beppu, *Exper. Cell Res.*, **177**: 122-131 (1988), teaches that TSA causes arrest of rat fibroblasts at the G<sub>1</sub> and G<sub>2</sub> phases of the cell cycle, implicating HDAC in cell cycle regulation.

Indeed, Finnin *et al.*, *Nature*, **401**: 188-193 (1999), teaches that TSA and SAHA inhibit cell growth, induce terminal differentiation, and prevent the formation of tumors in mice. Suzuki *et al.*, U.S. Pat. No. 6,174,905, EP 0847992, JP 258863/96, and Japanese Application No.

10138957, disclose benzamide derivatives that induce cell differentiation and inhibit HDAC.

Delorme *et al.*, WO 01/38322 and WO 01/70675, as well as Moradei *et al.*, WO 05/030704 and WO 05/030705, disclose additional compounds that serve as HDAC inhibitors.

[0007] The molecular cloning of gene sequences encoding proteins with HDAC activity has established the existence of a set of discrete HDAC enzyme isoforms. Some isoforms have been shown to possess specific functions, for example, it has been shown that HDAC-6 is involved in modulation of microtubule activity. However, the role of the other individual HDAC enzymes has remained unclear.

[0008] These findings suggest that inhibition of HDAC activity represents a novel approach for intervening in cell cycle regulation and that HDAC inhibitors have great therapeutic potential in the treatment of cell proliferative diseases or conditions. It would thus be desirable to have new inhibitors of histone deacetylase.

#### BRIEF SUMMARY OF THE INVENTION

[0009] Ortho-amino benzamides are known HDAC inhibitors. Substitutions at the ortho- and meta- positions relative to the amino group are detrimental to the potency of the inhibitors; however, some small substituents such as -CH<sub>3</sub>, -F, or -OCH<sub>3</sub> can be tolerated to a certain extent. We have found that *o*-amino benzamide HDAC inhibitors having a much bigger but flat aromatic

and heteroaromatic substituents such as phenyl, furyl, thienyl and the like para to the amino moiety are not only well tolerated but cause significant increase in HDAC inhibitory activity.

[0010] Accordingly, the present invention provides new compounds and methods for treating cell proliferative diseases. The invention provides new inhibitors of histone deacetylase enzymatic activity.

[0011] In a first aspect, the invention provides compounds that are useful as inhibitors of histone deacetylase.

[0012] In a second aspect, the invention provides a composition comprising an inhibitor of histone deacetylase according to the invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, excipient, or diluent.

[0013] In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase of the invention.

[0014] The foregoing merely summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below. All publications (patent or other) are hereby incorporated by reference in their entirety; in the event of any conflict between these materials and the present specification, the present specification shall control.

#### **DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

[0015] The invention provides compounds and methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions. The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure will prevail.

[0016] For purposes of the present invention, the following definitions will be used (unless expressly stated otherwise):

[0017] As used herein, the terms "histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from amino groups of lysine residues at the *N*-terminus of a protein, including but not limited to, a histone. Unless otherwise indicated



by context, the term "histone" is meant to refer to any histone protein, including H1, H2A, H2B, H3, H4, and H5, from any species. Preferred histone deacetylases include class I and class II enzymes. Preferably the histone deacetylase is a human HDAC, including, but not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, HDAC-9, HDAC-10, and HDAC-11. In some other preferred embodiments, the histone deacetylase is derived from a protozoal or fungal source.

**[0018]** The terms "histone deacetylase inhibitor" and "inhibitor of histone deacetylase" are used to identify a compound having a structure as defined herein, which is capable of interacting with a histone deacetylase and inhibiting its enzymatic activity. "Inhibiting histone deacetylase enzymatic activity" means reducing the ability of a histone deacetylase to remove an acetyl group from a protein, including but not limited to, a histone. In some preferred embodiments, such reduction of histone deacetylase activity is at least about 50%, more preferably at least about 75%, and still more preferably at least about 90%. In other preferred embodiments, histone deacetylase activity is reduced by at least 95% and more preferably by at least 99%.

**[0019]** Preferably, such inhibition is specific, i.e., the histone deacetylase inhibitor reduces the ability of a histone deacetylase to remove an acetyl group from a protein, including but not limited to, a histone, at a concentration that is lower than the concentration of the inhibitor that is required to produce another, unrelated biological effect. Preferably, the concentration of the inhibitor required for histone deacetylase inhibitory activity is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological effect.

**[0020]** For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (*e.g.*, alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety generally refers to a monovalent radical (*e.g.* CH<sub>3</sub>-CH<sub>2</sub>-), in certain circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (*e.g.*, -CH<sub>2</sub>-CH<sub>2</sub>-), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (*i.e.*, 4 for carbon, 3 for

N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). On occasion a moiety may be defined, for example, as  $(A)_a-B-$ , wherein  $a$  is 0 or 1. In such instances, when  $a$  is 0 the moiety is  $B-$  and when  $a$  is 1 the moiety is  $A-B-$ .

**[0021]** For simplicity, reference to a “ $C_n-C_m$ ” heterocyclyl or “ $C_n-C_m$ ” heteroaryl means a heterocyclyl or heteroaryl having from “ $n$ ” to “ $m$ ” annular atoms, where “ $n$ ” and “ $m$ ” are integers. Thus, for example, a  $C_5-C_6$ -heterocyclyl is a 5- or 6- membered ring having at least one heteroatom, and includes pyrrolidinyl ( $C_5$ ) and piperidinyl ( $C_6$ );  $C_6$ -heteroaryl includes, for example, pyridyl and pyrimidyl.

**[0022]** The term “hydrocarbyl” refers to a straight, branched, or cyclic alkyl, alkenyl, or alkynyl, each as defined herein. A “ $C_0$ ” hydrocarbyl is used to refer to a covalent bond. Thus, “ $C_0-C_3$ -hydrocarbyl” includes a covalent bond, methyl, ethyl, ethenyl, ethynyl, propyl, propenyl, propynyl, and cyclopropyl.

**[0023]** The term “alkyl” as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms, preferably 1-8 carbon atoms, and more preferably 1-6 carbon atoms. Preferred alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl. A “ $C_0$ ” alkyl (as in “ $C_0-C_3$ -alkyl”) is a covalent bond (like “ $C_0$ ” hydrocarbyl).

**[0024]** The term “alkenyl” as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms. Preferred alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

**[0025]** The term “alkynyl” as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms. Preferred alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

**[0026]** An “alkylene,” “alkenylene,” or “alkynylene” group is an alkyl, alkenyl, or alkynyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Preferred alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Preferred alkenylene groups include, without limitation, ethenylene, propenylene, and butenylene. Preferred alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

**[0027]** The term "cycloalkyl" is intended to mean a saturated or unsaturated mono-, bi, tri- or poly-cyclic (fused and/or spiro) hydrocarbon group having about 3 to 15 carbons, preferably having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons. In certain preferred embodiments, the cycloalkyl group is fused to an aryl, heteroaryl or heterocyclic group. Preferred cycloalkyl groups include, without limitation, cyclopenten-2-enone, cyclopenten-2-enol, cyclohex-2-enone, cyclohex-2-enol, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

**[0028]** In certain preferred embodiments, the cycloalkyl group is a bridged cycloalkyl group, preferably a C<sub>5</sub>-C<sub>10</sub> bridged bicyclic group. In certain preferred embodiments, the bridged cycloalkyl group is a C<sub>5</sub> bridged bicyclic group. In certain preferred embodiments, the bridged cycloalkyl group is a C<sub>6</sub> bridged bicyclic group. In certain preferred embodiments, the bridged cycloalkyl group is a C<sub>7</sub> bridged bicyclic group. In certain preferred embodiments, the bridged cycloalkyl group is a C<sub>8</sub> bridged bicyclic group. In certain preferred embodiments, the bridged cycloalkyl group is a C<sub>9</sub> bridged bicyclic. In certain preferred embodiments, the bridged cycloalkyl group has a bridge of 0, 1, 2 or 3 carbon atoms. A bridge of 0 carbon atoms is a bond, and equates to a cycloalkyl group fused to another ring structure. In certain preferred embodiments, the bridged cycloalkyl group has a bridge of 0, 1 or 3 carbon atoms. In certain preferred embodiments, the bridged cycloalkyl group has a bridge of 1 or 3 carbon atoms. In certain preferred embodiments, the bridged cycloalkyl group has a bridge of 1 carbon atom. In certain preferred embodiments, the bridged cycloalkyl group has a bridge of 2 carbon atoms. In certain preferred embodiments, the bridged cycloalkyl group has a bridge of 3 carbon atoms. If a bridged cycloalkyl group is described as "optionally substituted", it is intended to be optionally substituted on any position, including the bridge. The bridged cycloalkyl group is not limited to any particular stereochemistry.

**[0029]** The term "heteroalkyl" is intended to mean a saturated or unsaturated, straight or branched chain aliphatic group, wherein one or more carbon atoms in the chain are independently replaced by a heteroatom selected from the group consisting of O, S, and N.

**[0030]** The term "aryl" is intended to mean a mono-, bi-, tri- or polycyclic C<sub>6</sub>-C<sub>14</sub> aromatic moiety, preferably comprising one to three aromatic rings. Preferably, the aryl group is a C<sub>6</sub>-C<sub>10</sub> aryl group, more preferably a C<sub>6</sub> aryl group. Preferred aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl.

**[0031]** The terms “aralkyl” or “arylalkyl” are intended to mean a group comprising an aryl group covalently linked to an alkyl group. If an aralkyl group is described as “optionally substituted”, it is intended that either or both of the aryl and alkyl moieties may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is (C<sub>1</sub>-C<sub>6</sub>)alk(C<sub>6</sub>-C<sub>10</sub>)aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl. For simplicity, when written as “arylalkyl” this term, and terms related thereto, is intended to indicate the order of groups in a compound as “aryl – alkyl”. Similarly, “alkyl-aryl” is intended to indicate the order of the groups in a compound as “alkyl-aryl”.

**[0032]** The terms “heterocyclyl”, “heterocyclic” or “heterocycle” are intended to mean a group which is a mono-, bi-, or polycyclic structure having from about 3 to about 14 atoms, wherein one or more atoms are independently selected from the group consisting of N, O, and S. The ring structure may be saturated, unsaturated or partially unsaturated. In certain preferred embodiments, the heterocyclic group is non-aromatic. In a bicyclic or polycyclic structure, one or more rings may be aromatic; for example one ring of a bicyclic heterocycle or one or two rings of a tricyclic heterocycle may be aromatic, as in indan and 9,10-dihydro anthracene. Preferred heterocyclic groups include, without limitation, epoxy, aziridinyl, tetrahydrofuryl, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, oxazolidinonyl, and morpholino. In certain preferred embodiments, the heterocyclic group is fused to an aryl, heteroaryl, or cycloalkyl group. Examples of such fused heterocycles include, without limitation, tetrahydroquinoline and dihydrobenzofuran. Specifically excluded from the scope of this term are compounds where an annular O or S atom is adjacent to another O or S atom.

**[0033]** In certain preferred embodiments, the heterocyclic group is a bridged heterocyclic (or bridged heterocyclyl) group, preferably a C<sub>6</sub>-C<sub>10</sub> bridged bicyclic group, wherein one or more carbon atoms are independently replaced by a heteroatom selected from the group consisting of N, O and S. In certain preferred embodiments, the bridged heterocyclic group is a C<sub>6</sub> bridged bicyclic group. In certain preferred embodiments, the bridged heterocyclic group is a C<sub>7</sub> bridged bicyclic group. In certain preferred embodiments, the bridged heterocyclic group is a C<sub>8</sub> bridged bicyclic group. In certain preferred embodiments, the bridged heterocyclic group is a C<sub>9</sub> bridged bicyclic. In certain preferred embodiments, the bridged heterocyclic group has a bridge of 0, 1, 2 or 3 carbon atoms. In certain preferred embodiments, the bridged heterocyclic group has a bridge of 0, 1 or 3 carbon atoms. A bridge of 0 carbon atoms is a bond, and equates to a heterocyclic

group fused to another ring structure. In certain preferred embodiments, the bridged heterocyclic group has a bridge of 1 or 3 carbon atoms. In certain preferred embodiments, the bridged heterocyclic group has a bridge of 1 carbon atom. In certain preferred embodiments, the bridged heterocyclic group has a bridge of 2 carbon atoms. In certain preferred embodiments, the bridged heterocyclic group has a bridge of 3 carbon atoms. If a bridged heterocyclic group is described as “optionally substituted”, it is intended to be optionally substituted on any position, including the bridge. The bridged heterocyclic group is not limited to any particular stereochemistry.

**[0034]** In certain preferred embodiments, the heterocyclic group is a heteroaryl group. As used herein, the term “heteroaryl” is intended to mean a mono-, bi, tri or polycyclic group having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 pi electrons shared in a cyclic array; and having, in addition to carbon atoms, between one or more heteroatoms selected from the group consisting of N, O, and S. For example, a heteroaryl group may be pyrimidyl, pyridyl, benzimidazolyl, thienyl, benzothiazolyl, benzofuryl and indolyl. Preferred heteroaryl groups include, without limitation, thienyl, benzothienyl, furyl, benzofuryl, dibenzofuryl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, indolyl, quinolyl, isoquinolyl, quinoxalyl, tetrazolyl, oxazolyl, thiazolyl, and isoxazolyl. As used herein, the term “thienyl” is the same as the term “thiophenyl”.

**[0035]** A “heteroaralkyl” or “heteroarylalkyl” group comprises a heteroaryl group covalently linked to an alkyl group. If such a group is described as “optionally substituted”, it is intended that, either or both the “alkyl” or “heteroaryl” moieties may independently be optionally substituted or unsubstituted. Preferred heteroaralkyl groups comprise a C<sub>1</sub>-C<sub>6</sub> alkyl group and a heteroaryl group having 5, 6, 9, or 10 ring atoms. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms. Examples of preferred heteroaralkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, thiazolylmethyl, and thiazolylethyl.

**[0036]** An “arylene,” “heteroarylene,” or “heterocyclylene” group is an aryl, heteroaryl, or heterocyclyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

**[0037]** Preferred heterocyclyls and heteroaryls include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuryl, benzothiofuryl, benzothiophene, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benzotetrazolyl, benzisoxazolyl, benzisothiazolyl,

benzimidazoliny, carbazolyl, 4aH-carbazolyl, carboliny, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, 2H,6H-1,5,2-dithiaziny, dihydrofuro[2,3-b]tetrahydrofuran, furyl, furazanyl, imidazolidiny, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3H-indolyl, isobenzofuryl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny, oxazolyl, oxazolidiny, pyrimidyl, phenanthridiny, phenanthroliny, phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny, phthalaziny, piperaziny, piperidiny, piperidonyl, 4-piperidonyl, piperonyl, pteridiny, puriny, pyranyl, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridooxazole, pyridoimidazole, pyridothiazole, pyridyl, pyridyl, pyrrolidiny, pyrroliny, 2H-pyrrolyl, pyrrolyl, quinazoliny, quinoliny, 4H-quinoliziny, quinoxaliny, quinuclidiny, tetrahydrofuryl, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, 6H-1,2,5-thiadiaziny, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triaziny, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

**[0038]** As used herein, the term “pyridyl” is equivalent to the term “pyridiny”. Similarly, the term “pyrimidyl” is equivalent to the term “pyrimidiny”.

**[0039]** As employed herein, when a moiety (*e.g.*, cycloalkyl, hydrocarbyl, aryl, heteroaryl, heterocyclic, urea, etc.) is described as “optionally substituted” it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (*e.g.*, an annular -CH- substituted with oxo is -C(O)-) nitro, halohydrocarbyl, hydrocarbyl, heterocycle, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

**[0040]** (a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino,

**[0041]** (b) C<sub>1</sub>-C<sub>5</sub> alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> alkenyl, C<sub>1</sub>-C<sub>8</sub>

alkoxy, C<sub>1</sub>-C<sub>8</sub> alkoxycarbonyl, aryloxycarbonyl, C<sub>2</sub>-C<sub>8</sub> acyl, C<sub>2</sub>-C<sub>8</sub> acylamino, C<sub>1</sub>-C<sub>8</sub> alkylthio, arylalkylthio, arylthio, C<sub>1</sub>-C<sub>8</sub> alkylsulfinyl, arylalkylsulfinyl, arylsulfinyl, C<sub>1</sub>-C<sub>8</sub> alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C<sub>0</sub>-C<sub>6</sub> *N*-alkyl carbamoyl, C<sub>2</sub>-C<sub>15</sub> *N,N*-dialkylcarbamoyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C<sub>3</sub>-C<sub>7</sub> heterocycle, C<sub>5</sub>-C<sub>15</sub> heteroaryl or any of these rings fused or spiro-fused to a cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; and

**[0042]** (c)  $-(CR^{32}R^{33})_s-NR^{30}R^{31}$ , wherein *s* is an integer from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6; R<sup>32</sup> and R<sup>33</sup> are each independently hydrogen, halo, hydroxyl, aryl, heteroaryl, cycloalkyl, heterocyclyl or C<sub>1</sub>-C<sub>4</sub>alkyl; and R<sup>30</sup> and R<sup>31</sup> are each independently hydrogen, cyano, oxo, hydroxyl, -C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> heteroalkyl, C<sub>1</sub>-C<sub>8</sub> alkenyl, carboxamido, C<sub>1</sub>-C<sub>3</sub> alkyl-carboxamido, carboxamido-C<sub>1</sub>-C<sub>3</sub> alkyl, amidino, C<sub>2</sub>-C<sub>8</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub> alkylaryl, aryl-C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkylheteroaryl, heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkylheterocyclyl, heterocyclyl-C<sub>1</sub>-C<sub>3</sub> alkyl C<sub>1</sub>-C<sub>3</sub> alkylcycloalkyl, cycloalkyl-C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkoxy, C<sub>2</sub>-C<sub>8</sub> alkoxy-C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>8</sub> alkoxycarbonyl, aryloxycarbonyl, aryl-C<sub>1</sub>-C<sub>3</sub> alkoxycarbonyl, heteroaryloxycarbonyl, heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkoxycarbonyl, C<sub>1</sub>-C<sub>8</sub> acyl, C<sub>0</sub>-C<sub>8</sub> alkyl-carbonyl, aryl-C<sub>0</sub>-C<sub>8</sub> alkyl-carbonyl, heteroaryl-C<sub>0</sub>-C<sub>8</sub> alkyl-carbonyl, cycloalkyl-C<sub>0</sub>-C<sub>8</sub> alkyl-carbonyl, C<sub>0</sub>-C<sub>8</sub> alkyl-NH-carbonyl, aryl-C<sub>0</sub>-C<sub>8</sub> alkyl-NH-carbonyl, heteroaryl-C<sub>0</sub>-C<sub>8</sub> alkyl-NH-carbonyl, cycloalkyl-C<sub>0</sub>-C<sub>8</sub> alkyl-NH-carbonyl, C<sub>0</sub>-C<sub>8</sub> alkyl-O-carbonyl, aryl-C<sub>0</sub>-C<sub>8</sub> alkyl-O-carbonyl, heteroaryl-C<sub>0</sub>-C<sub>8</sub> alkyl-O-carbonyl, cycloalkyl-C<sub>0</sub>-C<sub>8</sub> alkyl-O-carbonyl, C<sub>1</sub>-C<sub>8</sub> alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, heteroarylalkylsulfonyl, heteroarylsulfonyl, C<sub>1</sub>-C<sub>8</sub> alkyl-NH-sulfonyl, arylalkyl-NH-sulfonyl, aryl-NH-sulfonyl, heteroarylalkyl-NH-sulfonyl, heteroaryl-NH-sulfonyl aroyl, aryl, cycloalkyl, heterocyclyl, heteroaryl, aryl-C<sub>1</sub>-C<sub>3</sub> alkyl-, cycloalkyl- C<sub>1</sub>-C<sub>3</sub> alkyl-, heterocyclyl- C<sub>1</sub>-C<sub>3</sub> alkyl-, heteroaryl- C<sub>1</sub>-C<sub>3</sub> alkyl-, or a protecting group, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; or

**[0043]** R<sup>30</sup> and R<sup>31</sup> taken together with the N to which they are attached form a heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents selected from the group consisting of (a) above, a protecting group, and

(X<sup>30</sup>-Y<sup>31</sup>-), wherein said heterocyclyl may also be bridged (forming a bicyclic moiety with a methylene, ethylene or propylene bridge); wherein

**[0044]** X<sup>30</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl-, C<sub>2</sub>-C<sub>8</sub>alkynyl-, -C<sub>0</sub>-C<sub>3</sub>alkyl -C<sub>2</sub>-C<sub>8</sub>alkenyl-C<sub>0</sub>-C<sub>3</sub>alkyl, C<sub>0</sub>-C<sub>3</sub>alkyl-C<sub>2</sub>-C<sub>8</sub>alkynyl-C<sub>0</sub>-C<sub>3</sub>alkyl, C<sub>0</sub>-C<sub>3</sub>alkyl-O-C<sub>0</sub>-C<sub>3</sub>alkyl-, HO-C<sub>0</sub>-C<sub>3</sub>alkyl-, C<sub>0</sub>-C<sub>4</sub>alkyl-N(R<sup>30</sup>)-C<sub>0</sub>-C<sub>3</sub>alkyl-, N(R<sup>30</sup>)(R<sup>31</sup>)-C<sub>0</sub>-C<sub>3</sub>alkyl-, N(R<sup>30</sup>)(R<sup>31</sup>)-C<sub>0</sub>-C<sub>3</sub>alkenyl-, N(R<sup>30</sup>)(R<sup>31</sup>)-C<sub>0</sub>-C<sub>3</sub>alkynyl-, (N(R<sup>30</sup>)(R<sup>31</sup>))<sub>2</sub>-C=N-, C<sub>0</sub>-C<sub>3</sub>alkyl-S(O)<sub>0-2</sub>-C<sub>0</sub>-C<sub>3</sub>alkyl-, CF<sub>3</sub>-C<sub>0</sub>-C<sub>3</sub>alkyl-, C<sub>1</sub>-C<sub>8</sub>heteroalkyl, aryl, cycloalkyl, heterocyclyl, heteroaryl, aryl-C<sub>1</sub>-C<sub>3</sub>alkyl-, cycloalkyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, heterocyclyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, heteroaryl-C<sub>1</sub>-C<sub>3</sub>alkyl-, N(R<sup>30</sup>)(R<sup>31</sup>)-heterocyclyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, wherein the aryl, cycloalkyl, heteroaryl and heterocyclyl are optionally substituted with from 1 to 3 substituents from (a); and

**[0045]** Y<sup>31</sup> is selected from the group consisting of a direct bond, -O-, -N(R<sup>30</sup>)-, -C(O)-, -O-C(O)-, -C(O)-O-, -N(R<sup>30</sup>)-C(O)-, -C(O)-N(R<sup>30</sup>)-, -N(R<sup>30</sup>)-C(S)-, -C(S)-N(R<sup>30</sup>)-, -N(R<sup>30</sup>)-C(O)-N(R<sup>31</sup>)-, -N(R<sup>30</sup>)-C(NR<sup>30</sup>)-N(R<sup>31</sup>)-, -N(R<sup>30</sup>)-C(NR<sup>31</sup>)-, -C(NR<sup>31</sup>)-N(R<sup>30</sup>), -N(R<sup>30</sup>)-C(S)-N(R<sup>31</sup>)-, -N(R<sup>30</sup>)-C(O)-O-, -O-C(O)-N(R<sup>31</sup>)-, -N(R<sup>30</sup>)-C(S)-O-, -O-C(S)-N(R<sup>31</sup>)-, -S(O)<sub>0-2</sub>-, -SO<sub>2</sub>N(R<sup>31</sup>)-, -N(R<sup>31</sup>)-SO<sub>2</sub>- and -N(R<sup>30</sup>)-SO<sub>2</sub>N(R<sup>31</sup>)-.

**[0046]** As a non-limiting example, substituted phenyls include 2-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluoro-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4-dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl. Included within this definition are methylenes (-CH<sub>2</sub>-) substituted with oxygen to form carbonyl -CO-.

**[0047]** When there are two optional substituents bonded to adjacent atoms of a ring structure, such as for example phenyl, thienyl, or pyridyl, the substituents, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heterocycle having 1, 2, or 3 annular heteroatoms.

**[0048]** In a preferred embodiment, hydrocarbyl, heteroalkyl, heterocyclic and aryl groups are unsubstituted.

**[0049]** In other preferred embodiments, hydrocarbyl, heteroalkyl, heterocyclic and aryl groups are substituted with from 1 to 3 independently selected substituents.



**[0050]** Preferred substituents on alkyl groups include, but are not limited to, hydroxyl, halogen (e.g., a single halogen substituent or multiple halo substituents; in the latter case, groups such as CF<sub>3</sub> or an alkyl group bearing Cl<sub>3</sub>), cyano, nitro, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, -OR<sup>u</sup>, -SR<sup>u</sup>, -S(=O)R<sup>y</sup>, -S(=O)<sub>2</sub>R<sup>y</sup>, -P(=O)<sub>2</sub>R<sup>y</sup>, -S(=O)<sub>2</sub>OR<sup>y</sup>, -P(=O)<sub>2</sub>OR<sup>y</sup>, -NR<sup>v</sup>R<sup>w</sup>, -NR<sup>v</sup>S(=O)<sub>2</sub>R<sup>y</sup>, -NR<sup>v</sup>P(=O)<sub>2</sub>R<sup>y</sup>, -S(=O)<sub>2</sub>NR<sup>v</sup>R<sup>w</sup>, -P(=O)<sub>2</sub>NR<sup>v</sup>R<sup>w</sup>, -C(=O)OR<sup>y</sup>, -C(=O)R<sup>u</sup>, -C(=O)NR<sup>v</sup>R<sup>w</sup>, -OC(=O)R<sup>u</sup>, -OC(=O)NR<sup>v</sup>R<sup>w</sup>, -NR<sup>v</sup>C(=O)OR<sup>y</sup>, -NR<sup>x</sup>C(=O)NR<sup>v</sup>R<sup>w</sup>, -NR<sup>x</sup>S(=O)<sub>2</sub>NR<sup>v</sup>R<sup>w</sup>, -NR<sup>x</sup>P(=O)<sub>2</sub>NR<sup>v</sup>R<sup>w</sup>, -NR<sup>v</sup>C(=O)R<sup>u</sup> or -NR<sup>v</sup>P(=O)<sub>2</sub>R<sup>y</sup>, wherein R<sup>u</sup> is hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle or aryl; R<sup>v</sup>, R<sup>w</sup> and R<sup>x</sup> are independently hydrogen, alkyl, cycloalkyl, heterocycle or aryl, or said R<sup>v</sup> and R<sup>w</sup> together with the N to which they are bonded optionally form a heterocycle; and R<sup>y</sup> is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle or aryl. In the aforementioned exemplary substituents, groups such as alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, heterocycle and aryl can themselves be optionally substituted.

**[0051]** Preferred substituents on alkenyl and alkynyl groups include, but are not limited to, alkyl or substituted alkyl, as well as those groups recited as preferred alkyl substituents.

**[0052]** Preferred substituents on cycloalkyl groups include, but are not limited to, nitro, cyano, alkyl or substituted alkyl, as well as those groups recited about as preferred alkyl substituents. Other preferred substituents include, but are not limited to, spiro-attached or fused cyclic substituents, preferably spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

**[0053]** Preferred substituents on cycloalkenyl groups include, but are not limited to, nitro, cyano, alkyl or substituted alkyl, as well as those groups recited as preferred alkyl substituents. Other preferred substituents include, but are not limited to, spiro-attached or fused cyclic substituents, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

**[0054]** Preferred substituents on aryl groups include, but are not limited to, nitro, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, cyano, alkyl or substituted

alkyl, as well as those groups recited above as preferred alkyl substituents. Other preferred substituents include, but are not limited to, fused cyclic groups, especially fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted. Still other preferred substituents on aryl groups (phenyl, as a non-limiting example) include, but are not limited to, haloalkyl and those groups recited as preferred alkyl substituents.

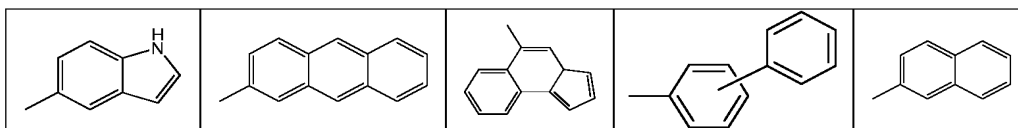
**[0055]** Preferred substituents on heterocyclic groups include, but are not limited to, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, nitro, oxo (*i.e.*, =O), cyano, alkyl, substituted alkyl, as well as those groups recited as preferred alkyl substituents. Other preferred substituents on heterocyclic groups include, but are not limited to, spiro-attached or fused cyclic substituents at any available point or points of attachment, more preferably spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle and fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

**[0056]** In a preferred embodiment, a heterocyclic group is substituted on carbon, nitrogen and/or sulfur at one or more positions. Preferred substituents on nitrogen include, but are not limited to N-oxide, alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, or aralkoxycarbonyl. Preferred substituents on sulfur include, but are not limited to, oxo and C<sub>1-6</sub>alkyl. In certain preferred embodiments, nitrogen and sulfur heteroatoms may independently be optionally oxidized and nitrogen heteroatoms may independently be optionally quaternized.

**[0057]** Especially preferred substituents on alkyl groups include halogen and hydroxy.

**[0058]** Especially preferred substituents on ring groups, such as aryl, heteroaryl, cycloalkyl and heterocyclyl, include halogen, alkoxy and alkyl.

**[0059]** In addition, preferred substituents on cyclic moieties (*i.e.*, cycloalkyl, heterocyclyl, aryl, heteroaryl) include 5-6 membered mono- and 9-14 membered bi-cyclic moieties fused to the parent cyclic moiety to form a bi- or tri-cyclic fused ring system. Substituents on cyclic moieties also include 5-6 membered mono- and 9-14 membered bi-cyclic moieties attached to the parent cyclic moiety by a covalent bond to form a bi- or tri-cyclic bi-ring system. For example, an optionally substituted phenyl includes, but not limited to, the following:



**[0060]** A “halohydrocarbyl” is a hydrocarbyl moiety in which from one to all hydrogens have been replaced with one or more halo. Similarly, “haloalkyl” is an alkyl moiety in which from one to all hydrogens have each been replaced with a halo.

**[0061]** The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine. As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent. The term "acylamino" refers to an amide group attached at the nitrogen atom (*i.e.*, R-CO-NH-). The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom (*i.e.*, NH<sub>2</sub>-CO-). The nitrogen atom of an acylamino or carbamoyl substituent is additionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom. The term "amino" is meant to include NH<sub>2</sub>, alkylamino, di-alkylamino, arylamino, and cyclic amino groups. The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

**[0062]** The term “radical” as used herein means a chemical moiety comprising one or more unpaired electrons.

**[0063]** An “unsubstituted” moiety as defined above (*e.g.*, unsubstituted cycloalkyl, unsubstituted heteroaryl, etc.) means that moiety as defined above that does not have any of the optional substituents for which the definition of the moiety (above) otherwise provides. Thus, for example, “unsubstituted aryl” does not include phenyl substituted with a halo.

**[0064]** Throughout the specification preferred embodiments of one or more chemical substituents are identified. Also preferred are combinations of preferred embodiments.

**[0065]** The term “protecting group” is intended to mean a group used in synthesis to temporarily mask the characteristic chemistry of a functional group because it interferes with another reaction. A good protecting group should be easy to put on, easy to remove and in high yielding reactions, and inert to the conditions of the reaction required. A protecting group or protective group is introduced into a molecule by chemical modification of a functional group in order to obtain chemoselectivity in a subsequent chemical reaction. One skilled in the art will recognize that during any of the processes for preparation of the compounds in the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of

the molecules concerned. This may be achieved by means of conventional protecting groups, such as but not limited to Bn- (or -CH<sub>2</sub>Ph), -CHPh<sub>2</sub>, alloc (or CH<sub>2</sub>=CH-CH<sub>2</sub>-O-C(O)-), BOC-, -Cbz (or Z-), -F-moc, -C(O)-CF<sub>3</sub>, N-Phthalimide, 1-Adoc-, TBDMS-, TBDPS-, TMS-, TIPS-, IPDMS-, -SiR<sub>3</sub>, SEM-, t-Bu-, Tr-, THP- and Allyl-. These protecting groups may be removed at a convenient stage using methods known from the art.

**[0066]** Some compounds of the invention may have chiral centers and/or geometric isomeric centers (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers. The invention also comprises all tautomeric forms of the compounds disclosed herein. Where compounds of the invention include chiral centers, the invention encompasses the enantiomerically pure isomers of such compounds, the enantiomerically enriched mixtures of such compounds, and the racemic and scalemic mixtures of such compounds. Preferably in enantiomerically enriched mixtures there is greater or equal to 80% of one enantiomer, more preferably greater than 90%, 95%, or 98%.

**[0067]** The present invention also includes prodrugs of compounds of the invention. The term "prodrug" is intended to represent covalently bonded carriers, which are capable of releasing the active ingredient when the prodrug is administered to a mammalian subject. Release of the active ingredient occurs *in vivo*. Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups however regenerate original functional groups by routine manipulation or *in vivo*. Prodrugs of compounds of the invention include compounds wherein a hydroxy, amino, carboxylic, or a similar group is modified. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy or amino functional groups in compounds of Formula (I), amides (e.g., trifluoroacetyl amino, acetyl amino, and the like), and the like.

**[0068]** The compounds of the invention may be administered as is or as a prodrug, for example in the form of an *in vivo* hydrolyzable ester or *in vivo* hydrolyzable amide. An *in vivo* hydrolyzable ester of a compound of the invention containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolyzed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C<sub>1-6</sub>-alkoxymethyl esters (e.g., methoxymethyl), C<sub>1-6</sub>-alkanoyloxymethyl esters (e.g., for example pivaloyloxymethyl), phthalidyl esters, C<sub>3-8</sub>-cycloalkoxycarbonyloxyC<sub>1-6</sub>-alkyl esters

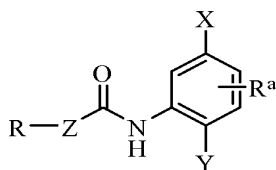
(e.g., 1-cyclohexylcarbonyloxyethyl); 1,3-dioxolen-2-onylmethyl esters (e.g., 5-methyl-1,3-dioxolen-2-onylmethyl; and C<sub>1-6</sub>-alkoxycarbonyloxyethyl esters (e.g., 1-methoxycarbonyloxyethyl) and may be formed at any carboxy group in the compounds of this invention.

**[0069]** An *in vivo* hydrolyzable ester of a compound of the invention containing a hydroxy group includes inorganic esters such as phosphate esters and  $\alpha$ -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of  $\alpha$ -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolyzable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxy carbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(*N,N*-dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), *N,N*-dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring. A suitable value for an *in vivo* hydrolyzable amide of a compound of the invention containing a carboxy group is, for example, a *N*-C<sub>1-6</sub>-alkyl or *N,N*-di-C<sub>1-6</sub>-alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N,N*-dimethyl, *N*-ethyl-*N*-methyl or *N,N*-diethyl amide.

**[0070]** The foregoing merely summarizes some aspects and preferred embodiments thereof and is not intended to be limiting in nature. These aspects and preferred embodiments thereof are described more fully below.

## Compounds

**[0071]** In one aspect, the invention comprises compounds of formula I:



**[0072]** and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof, and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

**[0073]** in embodiment (I):

**[0074]** X is phenyl, thienyl, pyridyl, or pyrimidyl, each of which is optionally substituted with one to three substituents independently selected from halo, -CN, -CH=N(OH), hydroxy, C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl, -O-C<sub>1</sub>-C<sub>4</sub>alkyl, -(CH<sub>2</sub>)<sub>0-3</sub>-N(R<sup>3</sup>)(R<sup>4</sup>), methoxy, or mono-, di-, or tri- halo substituted alkyl, or, when there are two optional substituents bonded to adjacent atoms of the phenyl, thienyl, or pyridyl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heterocycle having 1, 2, or 3 annular heteroatoms, which cycloalkyl or heterocycle is optionally substituted with oxo, alkyl and -C(O)-O-alkyl-heteroaryl;

**[0075]** Y is -NH<sub>2</sub> or OH;

**[0076]** R<sup>a</sup> is H or halo (preferably F);

**[0077]** Z is selected from the group consisting of a bond, phenyl, furyl, benzofuryl, pyridyl, -C<sub>1</sub>-C<sub>3</sub>alkyl-phenyl, -phenyl-C<sub>1</sub>-C<sub>3</sub>alkyl-heterocyclyl, -phenyl-alkenyl-, -phenyl-alkyl-, heterocyclyl and cycloalkyl, each of which is optionally substituted with C<sub>1</sub>-C<sub>3</sub>alkyl, -OMe or halo;

**[0078]** R is selected from the group consisting of H, -(CH<sub>2</sub>)<sub>0-3</sub>-N(R<sup>3</sup>)(R<sup>4</sup>), -(CH<sub>2</sub>)-C(O)-N(R<sup>3</sup>)(R<sup>4</sup>), -(CH<sub>2</sub>)<sub>0-2</sub>-C(O)-O-(CH<sub>2</sub>)<sub>2-3</sub>-N(R<sup>3</sup>)(R<sup>4</sup>), -(CH<sub>2</sub>)<sub>0-2</sub>-C(O)O-(CH<sub>2</sub>)<sub>0-3</sub>-heteroaryl, -(CH<sub>2</sub>)<sub>0-2</sub>-C(O)-O-(CH<sub>2</sub>)<sub>0-3</sub>-aryl, -SO<sub>2</sub>-(CH<sub>2</sub>)<sub>0-3</sub>-aryl, -SO<sub>2</sub>-N(R<sup>3</sup>)(R<sup>4</sup>), -SO<sub>2</sub>-(CH<sub>2</sub>)<sub>0-3</sub>-heteroaryl, -SO<sub>2</sub>-(CH<sub>2</sub>)<sub>0-3</sub>-heterocyclyl, indole, cycloocta-inole, -(CH<sub>2</sub>)<sub>2-3</sub>-heterocyclyl, -(CH<sub>2</sub>)<sub>0-3</sub>-aryl, -(CH<sub>2</sub>)<sub>0-3</sub>-heteroaryl, -(CH<sub>2</sub>)<sub>1-3</sub>-O-C(O)-C<sub>1-6</sub>alkyl (wherein the alkyl is optionally substituted with a moiety selected from the group consisting of -N(R<sup>30</sup>)(R<sup>31</sup>), -(CR<sup>32</sup>R<sup>33</sup>)<sub>3</sub>-N(R<sup>30</sup>)(R<sup>31</sup>), -Y<sup>31</sup>-X<sup>30</sup>, and -O-(CH<sub>2</sub>)<sub>2-3</sub>-N(R<sup>3</sup>)(R<sup>4</sup>), and wherein the aryl, heteroaryl, heterocyclyl are each optionally substituted; or

**[0079]** -Z-R is selected from the group consisting -C<sub>1</sub>-C<sub>8</sub>alkyl, -phenyl-heterocyclyl, -phenyl-dibenzo-oxazepine, -benzofuryl-heterocyclyl, -benzofuryl-O-(CH<sub>2</sub>)<sub>2-3</sub>-heterocyclyl, -benzothienyl-O-(CH<sub>2</sub>)<sub>2-3</sub>-heterocyclyl, or -benzofuryl -O-(CH<sub>2</sub>)<sub>2-3</sub>-N(R<sup>3</sup>)(R<sup>4</sup>), each of which is optionally substituted; and

**[0080]** R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of H, -C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>2</sub>-C<sub>3</sub> alkyl-OR<sup>5</sup>, aryl, heteroaryl, -heteroaryl-heteroaryl, -heteroaryl-aryl, -aryl-heteroaryl, -C(O)-aryl, -C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl, -C<sub>2</sub>-C<sub>3</sub>alkyl-O-C<sub>1</sub>-C<sub>3</sub>alkyl, -C<sub>2</sub>-C<sub>3</sub>-alkyl-NR<sup>5</sup>R<sup>6</sup>, -CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>-NR<sup>5</sup>R<sup>6</sup>, wherein aryl and heteroaryl are optionally

substituted with one, two or three amino, methoxy, hydroxyl, -S-CH<sub>2</sub>-heteroaryl, -NR<sub>3</sub>S(O)<sub>2</sub>-C<sub>1</sub>-C<sub>3</sub>alkyl, or

**[0081]** R<sup>3</sup> and R<sup>4</sup>, together with the nitrogen to which they are both bonded, form a 4- or 6- membered heterocyclyl with 1 or 2 annular heteroatoms (including the nitrogen to which R<sup>3</sup> and R<sup>4</sup> are bonded), which heterocyclyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of H, hydroxy, oxo, amino, -N=C(NR<sup>3</sup>R<sup>4</sup>)<sub>2</sub>, one, two or three C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, heteroaryl, -C<sub>1</sub>-C<sub>6</sub> alkyl-aryl, -C<sub>1</sub>-C<sub>6</sub> alkyl-heteroaryl, -C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl, -C<sub>0</sub>-C<sub>3</sub>-alkyl-SR<sup>7</sup>, -C<sub>2</sub>-C<sub>3</sub>-alkyl-OH, -C<sub>2</sub>-C<sub>3</sub>-alkyl-O-C<sub>1</sub>-C<sub>4</sub>-alkyl, -C<sub>5</sub>-C<sub>6</sub>-cycloalkyl, -C<sub>0</sub>-C<sub>3</sub>-alkyl-N(R<sup>3</sup>)-C(O)-C<sub>1</sub>-C<sub>3</sub>alkyl, -C<sub>0,3</sub>alkyl-N(R<sup>3</sup>)-C(O)-thiomethyl, -C<sub>0</sub>-C<sub>3</sub>-alkyl-NR<sup>3</sup>C(O)O-C<sub>1</sub>-C<sub>3</sub>alkyl aryl, -C<sub>0</sub>-C<sub>3</sub>-alkyl-CF<sub>3</sub>, -C<sub>0</sub>-C<sub>3</sub>-alkyl-NR<sup>3</sup>C(O)O-C<sub>1</sub>-C<sub>3</sub>alkyl heteroaryl and -C<sub>0</sub>-C<sub>3</sub>-alkyl-N(R<sup>7</sup>)(R<sup>8</sup>), wherein said heterocyclyl is optionally fused to an aryl or heteroaryl;

**[0082]** R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, and R<sup>8</sup> are independently selected from -H, -C<sub>0</sub>-C<sub>3</sub>-alkyl-aryl, -C<sub>0</sub>-C<sub>3</sub>-alkyl-heteroaryl, -C<sub>0</sub>-C<sub>3</sub>-alkyl-heterocyclyl, -C<sub>0</sub>-C<sub>3</sub>-alkyl-cycloalkyl and C<sub>1</sub>-C<sub>6</sub>-alkyl;

**[0083]** s is an integer from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6;

**[0084]** R<sup>32</sup> and R<sup>33</sup> are each independently selected from the group consisting of hydrogen, halo, hydroxyl, -C<sub>0</sub>-C<sub>3</sub>alkyl-aryl, -C<sub>0</sub>-C<sub>3</sub>alkyl-heteroaryl, -C<sub>0</sub>-C<sub>3</sub>alkyl-heterocyclyl, -C<sub>0</sub>-C<sub>3</sub>alkyl-cycloalkyl and C<sub>1</sub>-C<sub>4</sub>alkyl;

**[0085]** R<sup>30</sup> and R<sup>31</sup> are each independently selected from the group consisting of hydrogen, cyano, oxo, hydroxyl, -C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>1</sub>-C<sub>8</sub>heteroalkyl, C<sub>1</sub>-C<sub>8</sub>alkenyl, carboxamido, C<sub>1</sub>-C<sub>3</sub>alkyl-carboxamido-, carboxamido-C<sub>1</sub>-C<sub>3</sub>alkyl-, amidino, C<sub>2</sub>-C<sub>8</sub>hydroxyalkyl-, C<sub>1</sub>-C<sub>3</sub>alkylaryl-, aryl-C<sub>1</sub>-C<sub>3</sub>alkyl-, C<sub>1</sub>-C<sub>3</sub>alkylheteroaryl-, heteroaryl-C<sub>1</sub>-C<sub>3</sub>alkyl-, C<sub>1</sub>-C<sub>3</sub>alkylheterocyclyl-, heterocyclyl-C<sub>1</sub>-C<sub>3</sub>alkyl, C<sub>1</sub>-C<sub>3</sub>alkylcycloalkyl-, cycloalkyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, C<sub>2</sub>-C<sub>8</sub>alkoxy, C<sub>2</sub>-C<sub>8</sub>alkoxy-C<sub>1</sub>-C<sub>4</sub>alkyl-, C<sub>1</sub>-C<sub>8</sub>alkoxycarbonyl-, aryloxy carbonyl, aryl-C<sub>1</sub>-C<sub>3</sub>alkoxycarbonyl-, heteroaryloxy carbonyl, heteroaryl-C<sub>1</sub>-C<sub>3</sub>alkoxycarbonyl-, C<sub>1</sub>-C<sub>8</sub>acyl, C<sub>0</sub>-C<sub>8</sub>alkyl-carbonyl-, aryl-C<sub>0</sub>-C<sub>8</sub>alkyl-carbonyl-, heteroaryl-C<sub>0</sub>-C<sub>8</sub>alkyl-carbonyl-, cycloalkyl-C<sub>0</sub>-C<sub>8</sub>alkyl-carbonyl-, C<sub>0</sub>-C<sub>8</sub>alkyl-NH-carbonyl-,

aryl-C<sub>0</sub>-C<sub>8</sub>alkyl-NH-carbonyl-, heteroaryl-C<sub>0</sub>-C<sub>8</sub>alkyl-NH-carbonyl-,  
 cycloalkyl-C<sub>0</sub>-C<sub>8</sub>alkyl-NH-carbonyl-, C<sub>0</sub>-C<sub>8</sub>alkyl-O-carbonyl-,  
 aryl-C<sub>0</sub>-C<sub>8</sub>alkyl-O-carbonyl-, heteroaryl-C<sub>0</sub>-C<sub>8</sub>alkyl-O-carbonyl-,  
 cycloalkyl-C<sub>0</sub>-C<sub>8</sub>alkyl-O-carbonyl-, C<sub>1</sub>-C<sub>8</sub>alkylsulfonyl-, arylalkylsulfonyl-, arylsulfonyl-,  
 heteroarylalkylsulfonyl-, heteroarylsulfonyl-, C<sub>1</sub>-C<sub>8</sub>alkyl-NH-sulfonyl-,  
 arylalkyl-NH-sulfonyl-, aryl-NH-sulfonyl-, heteroarylalkyl-NH-sulfonyl-,  
 heteroaryl-NH-sulfonyl-, aroyl, aryl, cycloalkyl, heterocyclyl, heteroaryl,  
 aryl-C<sub>1</sub>-C<sub>3</sub>alkyl-, cycloalkyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, heterocyclyl-C<sub>1</sub>-C<sub>3</sub>alkyl-,  
 heteroaryl-C<sub>1</sub>-C<sub>3</sub>alkyl- and a protecting group, wherein each of the foregoing is further  
 optionally substituted with one more moieties selected from halo, cyano, oxo, carboxy,  
 formyl, nitro, amino, amidino and guanidino; or

**[0086]** R<sup>30</sup> and R<sup>31</sup> taken together with the N to which they are attached form a  
 heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3  
 substituents selected from the group consisting of halo, cyano, oxo, carboxy, formyl,  
 nitro, amino, amidino, guanidino, a protecting group, and (X<sup>30</sup>-Y<sup>31</sup>-), wherein said  
 heterocyclyl may also be bridged (forming a bicyclic moiety with a methylene, ethylene  
 or propylene bridge);

**[0087]** X<sup>30</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>8</sub>alkyl-, C<sub>2</sub>-C<sub>8</sub>alkenyl-,  
 C<sub>2</sub>-C<sub>8</sub>alkynyl-, C<sub>0</sub>-C<sub>3</sub>alkyl-C<sub>2</sub>-C<sub>8</sub>alkenyl-C<sub>0</sub>-C<sub>3</sub>alkyl-,  
 C<sub>0</sub>-C<sub>3</sub>alkyl-C<sub>2</sub>-C<sub>8</sub>alkynyl-C<sub>0</sub>-C<sub>3</sub>alkyl-, C<sub>0</sub>-C<sub>3</sub>alkyl-O-C<sub>0</sub>-C<sub>3</sub>alkyl-, HO-C<sub>0</sub>-C<sub>3</sub>alkyl-,  
 C<sub>0</sub>-C<sub>4</sub>alkyl-N(R<sup>30</sup>)-C<sub>0</sub>-C<sub>3</sub>alkyl-, N(R<sup>30</sup>)(R<sup>31</sup>)-C<sub>0</sub>-C<sub>3</sub>alkyl-, N(R<sup>30</sup>)(R<sup>31</sup>)-C<sub>0</sub>-C<sub>3</sub>alkenyl-,  
 N(R<sup>30</sup>)(R<sup>31</sup>)-C<sub>0</sub>-C<sub>3</sub>alkynyl-, (N(R<sup>30</sup>)(R<sup>31</sup>))<sub>2</sub>-C=N-, C<sub>0</sub>-C<sub>3</sub>alkyl-S(O)<sub>0-2</sub>-C<sub>0</sub>-C<sub>3</sub>alkyl-,  
 CF<sub>3</sub>-C<sub>0</sub>-C<sub>3</sub>alkyl-, C<sub>1</sub>-C<sub>8</sub>heteroalkyl, aryl, cycloalkyl, heterocyclyl, heteroaryl,  
 aryl-C<sub>1</sub>-C<sub>3</sub>alkyl-, cycloalkyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, heterocyclyl-C<sub>1</sub>-C<sub>3</sub>alkyl-,  
 heteroaryl-C<sub>1</sub>-C<sub>3</sub>alkyl- and N(R<sup>30</sup>)(R<sup>31</sup>)-heterocyclyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, wherein the aryl,  
 cycloalkyl, heteroaryl and heterocyclyl are optionally substituted with from 1 to 3  
 substituents from halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino and guanidino;  
 and

**[0088]** Y<sup>31</sup> is selected from the group consisting of a direct bond, -O-, -N(R<sup>30</sup>)-,  
 -C(O)-, -O-C(O)-, -C(O)-O-, -N(R<sup>30</sup>)-C(O)-, -C(O)-N(R<sup>30</sup>)-, -N(R<sup>30</sup>)-C(S)-,  
 -C(S)-N(R<sup>30</sup>)-, -N(R<sup>30</sup>)-C(O)-N(R<sup>31</sup>)-, -N(R<sup>30</sup>)-C(NR<sup>30</sup>)-N(R<sup>31</sup>)-, -N(R<sup>30</sup>)-C(NR<sup>31</sup>)-,



-C(NR<sup>31</sup>)-N(R<sup>30</sup>), -N(R<sup>30</sup>)-C(S)-N(R<sup>31</sup>)-, -N(R<sup>30</sup>)-C(O)-O-, -O-C(O)-N(R<sup>31</sup>)-, -N(R<sup>30</sup>)-C(S)-O-, -O-C(S)-N(R<sup>31</sup>)-, -S(O)<sub>0-2</sub>-, -SO<sub>2</sub>N(R<sup>31</sup>)-, -N(R<sup>31</sup>)-SO<sub>2</sub>- and -N(R<sup>30</sup>)-SO<sub>2</sub>N(R<sup>31</sup>)-;

[0089] provided that Y<sup>31</sup> and X<sup>30</sup> are not linked to form -O-O- or -O-N-;

[0090] in embodiment (II):

[0091] X is thienyl (preferably thien-2-yl);

[0092] Y is -NH<sub>2</sub>;

[0093] Z is pyridyl (preferably pyrid-3-yl), furyl, heterocyclyl, or cycloalkyl; and

[0094] R is -C(=NH)(N(R<sup>3</sup>)(R<sup>4</sup>)), -C(NH<sub>2</sub>)(=NOMe), -C(NH<sub>2</sub>)(=NOH), -NR<sup>3</sup>SO<sub>2</sub>NR<sup>3</sup>R<sup>4</sup>, -C≡C-C<sub>1</sub>-C<sub>3</sub>alkyl-NR<sup>3</sup>R<sup>4</sup>, -C<sub>0</sub>-C<sub>3</sub>alkyl-aryl or -C<sub>0</sub>-C<sub>3</sub>alkyl-(5- or 6-membered heterocyclyl) optionally substituted with C<sub>1</sub>-C<sub>3</sub>-alkyl or -N(R<sup>3</sup>)(R<sup>4</sup>), wherein R<sup>3</sup> and R<sup>4</sup> are defined as in embodiment (I), above;

[0095] in embodiment (III):

[0096] X is thienyl (preferably thienyl-2-yl), phenyl or pyridyl, each of which is optionally substituted with C<sub>1</sub>-C<sub>3</sub>alkyl or halo;

[0097] Y is -NH<sub>2</sub>;

[0098] Z is phenyl, pyridyl (preferably pyrid-2-yl), furyl, thienyl, heterocyclyl, or cycloalkyl; and

[0099] R is an optionally substituted -C<sub>0</sub>-C<sub>3</sub>alkyl-aryl, -C(O)-aryl, -C<sub>0</sub>-C<sub>3</sub>alkyl-N(R<sup>3</sup>)-aryl, -C<sub>0</sub>-C<sub>3</sub>alkyl-(5- or 6- membered aryl or heteroaryl) (preferably optionally substituted with from 1 to 3 C<sub>1</sub>-C<sub>3</sub>-alkoxy);

[0100] wherein R<sup>3</sup> is defined as in embodiment (I), above

[0101] in embodiment (IV):

[0102] X is thienyl (preferably (thien-2-yl), phenyl, pyridyl, or pyridyl-N-oxide, wherein the thienyl may also be optionally substituted with halo or CN, and the phenyl and pyridyl moieties are optionally substituted with one or more halo;

[0103] Y is -NH<sub>2</sub>;

[0104] R<sup>a</sup> is H or F;

[0105] Z is aryl, 5- to 9- membered heterocyclyl, heteroaryl, or cycloalkyl, each of which is optionally substituted with one or two substituents selected from halo, oxo, CN, hydroxy, C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl, methoxy, or mono-, di-, or tri- halo substituted alkyl,

or, when there are two optional substituents bonded to adjacent atoms of the aryl, heteroaryl, or heterocyclyl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heterocycle having 1, 2, or 3 annular heteroatoms; and

**[0106]** R is H, halo, hydroxyl, C<sub>1</sub>-C<sub>3</sub>alkyl-OH, cyano, alkoxy, -C<sub>0</sub>-C<sub>3</sub>alkyl-N(R<sup>3</sup>)(R<sup>4</sup>), -C<sub>0</sub>-C<sub>3</sub>alkyl-N(R<sup>3</sup>)-C<sub>1</sub>-C<sub>3</sub>alkyl-CH(OH)-CH<sub>2</sub>OH, -C<sub>0</sub>-C<sub>2</sub>-alkyl-aryl or -C<sub>0</sub>-C<sub>2</sub>-alkyl-(5- or 6- membered heteroaryl or heterocyclyl), wherein the aryl, heteroaryl and heterocyclyl are optionally substituted with one to three independently selected moieties selected from the group consisting of methyl, halo, hydroxy, oxo-, -Y<sup>31</sup>-X<sup>30</sup>, or -(C R<sup>32</sup>R<sup>33</sup>)<sub>s</sub>-N(R<sup>30</sup>)(R<sup>31</sup>);

**[0107]** wherein R<sup>3</sup>, R<sup>4</sup>, R<sup>30</sup>, R<sup>31</sup>, R<sup>32</sup>, R<sup>33</sup>, s, Y<sup>31</sup> and X<sup>30</sup> are defined as in embodiment (I), above

**[0108]** in embodiment (V):

**[0109]** X is thienyl (preferably thien-2-yl);

**[0110]** Y is -NH<sub>2</sub>;

**[0111]** R<sup>a</sup> is H or F;

**[0112]** Z is phenyl, heterocyclyl or cycloalkyl;

**[0113]** R is -(CH<sub>2</sub>)-N(R<sup>3</sup>)(R<sup>4</sup>);

**[0114]** R<sup>3</sup> and R<sup>4</sup> are independently H, C<sub>1</sub>-C<sub>6</sub> alkyl, (5- or 6-membered heteroaryl)-C<sub>0</sub>-C<sub>2</sub>-alkyl; or

**[0115]** R<sup>3</sup> and R<sup>4</sup>, together with the nitrogen to which they are both bonded, form a 5- or 6- membered heterocyclyl with 1 or 2 annular heteroatoms (including the nitrogen to which R<sup>3</sup> and R<sup>4</sup> are bonded), which heterocyclyl is optionally substituted with at least one (preferably one, two, or three) moieties independently selected from hydroxy, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -N(R<sup>5</sup>)(R<sup>6</sup>), C<sub>1</sub>-C<sub>6</sub> alkoxyC<sub>1</sub>-C<sub>6</sub> alkyl, -NR<sup>7</sup>-C(O)-C<sub>1</sub>-C<sub>2</sub>-alkyl, NR<sup>7</sup>R<sup>8</sup>-C<sub>0</sub>-C<sub>3</sub>-alkyl, or (5- or 6-membered aryl, heterocyclyl or heteroaryl)-C<sub>0</sub>-C<sub>2</sub>-alkyl; and

**[0116]** R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, and R<sup>8</sup> are independently selected from -H and C<sub>1</sub>-C<sub>6</sub>-alkyl;

**[0117]** wherein R<sup>3</sup> and R<sup>4</sup> are defined as in embodiment (I), above

**[0118]** in embodiment (VI):

- [0119] X is thienyl (preferably thien-2-yl), thiazolyl, pyridyl, pyrimidyl or phenyl optionally substituted with one, two or three halo, amino or methoxy;
- [0120] Y is  $-\text{NH}_2$  or  $-\text{OH}$ ;
- [0121] Z is phenyl, heterocyclyl or cycloalkyl;
- [0122] R is  $\text{N}(\text{R}^3)(\text{R}^4)\text{-C}_0\text{-C}_1\text{-alkyl-}$  or  $\text{N}(\text{R}^5)(\text{R}^6)\text{-C}_1\text{-C}_3\text{-alkyl-S-}$ ,  $\text{N}(\text{R}^{30})(\text{R}^{31})\text{-(C R}^{32}\text{R}^{33})\text{s-}$ , or  $\text{X}^{30}\text{-Y}^{31}\text{-}$ ;
- [0123]  $\text{R}^3$  and  $\text{R}^4$  are independently  $-\text{H}$ ,  $-\text{C}_1\text{-C}_6$  alkyl,  $-\text{C}(\text{O})\text{-C}_0\text{-C}_3$  alkyl-aryl, aryl, -heteroaryl-aryl, -aryl-heteroaryl, aryl or heteroaryl and are optionally substituted with one, two or three halo,  $\text{CF}_3$ , amino or hydroxyl; or
- [0124]  $\text{R}^3$  and  $\text{R}^4$ , together with the nitrogen to which they are both bonded, form a 5- or 6- membered heterocyclyl with 1 or 2 annular heteroatoms (including the nitrogen to which  $\text{R}^3$  and  $\text{R}^4$  are bonded), which heterocyclyl is optionally substituted with  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_3\text{-alkoxy-C}_1\text{-C}_3\text{-alkyl-}$ ,  $-\text{N}=\text{C}(\text{NR}^3\text{R}^4)_2$ ,  $-\text{C}(\text{O})\text{O-C}_0\text{-C}_3\text{alkyl-aryl}$ ,  $-\text{C}(\text{O})\text{O-C}_0\text{-C}_3\text{alkyl-heteroaryl}$ , hydroxyl,  $-\text{N}(\text{R}^5)(\text{R}^6)$ ,  $-\text{C}_0\text{-C}_2\text{-alkyl-aryl}$ ,  $-\text{C}_0\text{-C}_2\text{-alkyl-(5- or 6-membered cycloalkyl, aryl, heterocyclyl or heteroaryl)}$ ,  $-\text{NH-aryl}$ , or  $-\text{NH-(5- or 6-membered cycloalkyl, heterocyclyl or heteroaryl)}$ ; and
- [0125]  $\text{R}^5$  and  $\text{R}^6$  are, independently,  $\text{H}$ ,  $-\text{C}_0\text{-C}_3\text{alkyl-aryl}$ , heteroaryl- $\text{C}_0\text{-C}_3\text{alkyl-heteroaryl}$ ,  $-\text{SO}_2\text{-Me}$ ,  $-\text{C}(\text{O})\text{-C}_1\text{-C}_4\text{alkyl}$  or  $\text{C}_1\text{-C}_3\text{-alkyl}$ ; wherein  $\text{R}^{30}$ ,  $\text{R}^{31}$ ,  $\text{R}^{32}$ ,  $\text{R}^{33}$ , s,  $\text{Y}^{31}$  and  $\text{X}^{30}$  are defined as in embodiment (I), above
- [0126] in embodiment (VII)
- [0127] X is thienyl (preferably thien-2-yl), phenyl, pyrimidyl or pyridyl;
- [0128] Y is  $-\text{NH}_2$ ;
- [0129]  $\text{R}^a$  is  $\text{H}$  or  $\text{F}$ ;
- [0130] Z is pyrimid-5-yl, heterocyclyl, or cycloalkyl;
- [0131] R is  $\text{C}_1\text{-C}_3\text{-alkoxy}$  or  $-\text{N}(\text{R}^3)(\text{R}^4)$ ; and
- [0132]  $\text{R}^3$  and  $\text{R}^4$ , together with the nitrogen to which they are both bonded, form a 5- or 6- membered heterocyclyl, or bridged heterocyclyl, with 1 or 2 annular heteroatoms (including the nitrogen to which  $\text{R}^3$  and  $\text{R}^4$  are bonded), which heterocyclyl is optionally substituted with amino, hydroxyl,  $\text{C}_1\text{-C}_6$  alkyl,  $-\text{C}_0\text{-C}_2\text{-alkyl-aryl}$  or  $-\text{C}_0\text{-C}_2\text{-alkyl-(5- or 6-membered cycloalkyl, heterocyclyl or heteroaryl)}$ , wherein the aryl

is optionally substituted with one to three independently selected substituents selected from the group consisting of halo, methoxy, CF<sub>3</sub>, CN and alkyl;

[0133] in embodiment (VIII):

[0134] X is aryl or a 5- or 6-membered heteroaryl optionally substituted with amino;

[0135] Y is -NH<sub>2</sub> or NHSO<sub>2</sub>NH<sub>2</sub>;

[0136] R<sup>a</sup> is H or F;

[0137] Z is phenyl, thienyl, heterocyclyl or cycloalkyl; and

[0138] R is C<sub>1</sub>-C<sub>3</sub>-alkoxy, aryl or a 5- or 6-membered heteroaryl;

[0139] in embodiment (IX):

[0140] X is aryl or 5- or 6-membered heteroaryl optionally substituted by one or two independently selected halo or CN;

[0141] Y is -NH<sub>2</sub>;

[0142] R<sup>a</sup> is H or F;

[0143] Z is phenyl, heterocyclyl or cycloalkyl; and

[0144] R is a -C<sub>0</sub>-C<sub>1</sub>-alkyl-(aryl, heteroaryl or 5-10-membered heterocyclyl) optionally substituted by methyl or oxo;

[0145] in embodiment (X):

[0146] X is thienyl;

[0147] Y is -NH<sub>2</sub>;

[0148] R<sup>a</sup> is H or F;

[0149] Z is phenyl, heterocyclyl or cycloalkyl;

[0150] R is R<sup>8</sup>-C(O)-C<sub>0</sub>-C<sub>3</sub>-alkyl- or Ac-NH-, and Z is further optionally substituted with -OH; and

[0151] R<sup>8</sup> is -OH, HO-NH-, or CH<sub>3</sub>-O-;

[0152] in embodiment (XI):

[0153] X is cyclopentenyl optionally substituted with oxo or hydroxy;

[0154] Y is -NH<sub>2</sub>;

[0155] R<sup>a</sup> is H or F;

[0156] Z is benzyl, -C<sub>0</sub>-C<sub>3</sub>alkyl-phenyl heterocyclyl or cycloalkyl; and

[0157] R is -C<sub>0</sub>-C<sub>3</sub>alkyl-morpholinyl;

[0158] in embodiment (XII):

[0159] X is aryl or 5- or 6-membered heteroaryl optionally substituted by one, two or three independently selected hydroxyl, -O-C<sub>1</sub>-C<sub>3</sub>alkyl, amino, -NR<sup>3</sup>R<sup>4</sup>, -CN, -CF<sub>3</sub>, -C<sub>1</sub>-C<sub>4</sub>alkyl, -S(O)<sub>0-2</sub>R<sup>5</sup>, -O-CF<sub>3</sub> or halo;

[0160] Y is -NH<sub>2</sub> or -OH;

[0161] R<sup>a</sup> is H or F;

[0162] Z is phenyl, heteroaryl, heterocyclyl, or cycloalkyl;

[0163] R is R<sup>9</sup>-(C<sub>0-6</sub>alkyl)N-C(O)-N(H)-(CH<sub>2</sub>)<sub>t</sub>, C<sub>0-6</sub>alkyl-S(O)<sub>2</sub>-N(H)-phenyl-C(O)-N(H)-(CH<sub>2</sub>)<sub>t</sub>, R<sup>9</sup>-O-C(O)-N(H)-(CH<sub>2</sub>)<sub>t</sub> or R<sup>9</sup>-O-C(O)-(CH<sub>2</sub>)<sub>t</sub>-wherein t is 0-2; and

[0164] R<sup>9</sup> is R<sup>10</sup>-C<sub>0</sub>-C<sub>2</sub>-alkyl-, wherein R<sup>10</sup> is aryl, 5- or 6-membered heterocyclyl or heteroaryl or N(X<sup>1</sup>)(X<sup>2</sup>)-C<sub>0-3</sub>alkyl- wherein X<sup>1</sup> and X<sup>2</sup> are independently H, C<sub>1</sub>-C<sub>4</sub>-alkyl or 5- or 6-membered heteroaryl, or X<sup>1</sup> and X<sup>2</sup>, together with the N to which they are bonded form a 5- or 6-membered heterocyclyl optionally substituted with methyl, which heterocyclyl and heteroaryl are optionally substituted with alkyl; provided that when R<sup>10</sup> is heterocyclyl attached through the N atoms, then R<sup>9</sup> is R<sup>10</sup>-C<sub>2</sub>-alkyl-;

[0165] wherein R<sup>3</sup> and R<sup>4</sup> are defined as in embodiment (I), above

[0166] in embodiment (XIII):

[0167] X is aryl or 5- or 6-membered cycloalkyl, heterocyclyl, or heteroaryl optionally substituted with hydroxy, oxo, or one or two halo;

[0168] Y is -OH or -NH<sub>2</sub>;

[0169] Z is phenyl, pyridyl, benzofuryl, heterocyclyl, or cycloalkyl optionally substituted with hydroxy, OMe or one or two halo, wherein when there are two optional substituents bonded to adjacent atoms of the phenyl, or benzofuryl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heteroalkyl having 1, 2, or 3 annular heteroatoms; and

[0170] R is -OH, -OMe, -O-C<sub>0</sub>-C<sub>3</sub>alkyl-heterocyclyl or -OAc; and

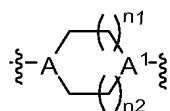
[0171] in embodiment (XIV):

[0172] X is thienyl;

[0173] Y is -NH<sub>2</sub>;

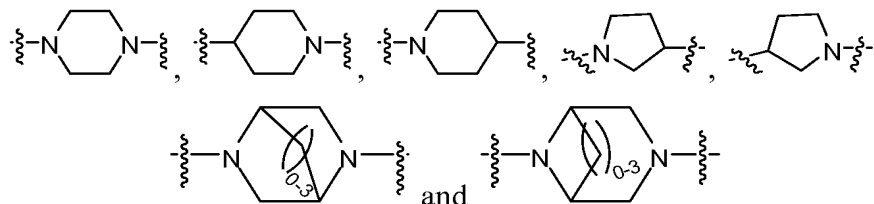
[0174] R<sup>a</sup> is H;

- [0175] Z is phenyl, heterocyclyl or cycloalkyl;
- [0176] R is  $R^{20}$ -C(O)-(C<sub>2</sub>-C<sub>3</sub>-alkyl or C<sub>2</sub>-C<sub>3</sub>-alkenyl)-; and
- [0177]  $R^{20}$  is HO-, HO-NH-, or MeO-;
- [0178] in embodiment (XV):
- [0179] X is pyridyl;
- [0180] Y is -NH<sub>2</sub>;
- [0181] R<sup>a</sup> is H or F;
- [0182] Z is phenyl, heterocyclyl, cycloalkyl or heteroaryl, wherein phenyl, heterocyclyl, cycloalkyl or heteroaryl are optionally substituted with hydroxy, alkyloxy, or halo; and
- [0183] R is -O-C<sub>0</sub>-C<sub>4</sub>-alkyl or -O-C<sub>2</sub>-C<sub>4</sub>-alkyl-heterocyclyl.
- [0184] in embodiment (XVI):
- [0185] X is aryl, -aryl-heteroaryl, heterocyclyl, -heteroaryl-aryl or heteroaryl, wherein said aryl or heteroaryl is optionally substituted;
- [0186] Y is NH<sub>2</sub>;
- [0187] R<sup>a</sup> is H or halogen;
- [0188] Z is benzofuryl, -benzofuryl-aryl, benzofuryl-heteroaryl, benzothiophene or phenyl, optionally substituted with one or more groups independently selected from C<sub>1</sub>-C<sub>7</sub>alkyl, hydroxy, C<sub>1</sub>-C<sub>7</sub>alkoxy, halo, CN and amino; and
- [0189] R is H, -(CR<sup>32</sup>R<sup>33</sup>)<sub>s</sub>-N(R<sup>30</sup>)(R<sup>31</sup>), -Y<sup>31</sup>-X<sup>30</sup>, -O-heterocyclyl, -O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(R<sup>30</sup>)(R<sup>31</sup>), -(CH<sub>2</sub>)<sub>s</sub>-N(R<sup>30</sup>)(R<sup>31</sup>) or -O-C<sub>1</sub>-C<sub>3</sub>alkyl;
- [0190] wherein R<sup>30</sup>, R<sup>31</sup>, R<sup>32</sup>, R<sup>33</sup>, s, Y<sup>31</sup> and X<sup>30</sup> are defined as in embodiment (I), above.
- [0191] In another aspect, the invention comprises compounds according to the previous embodiments- in which Z is

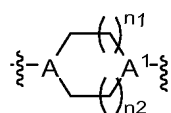


- [0192] wherein A and A<sup>1</sup> are independently CR<sup>11</sup> or N, wherein R<sup>11</sup> is -OH, alkyl, alkenyl, alkynyl or aryl, and n1 and n2 are each independently 0-3, provided that when n1 and n2 are 0, then A and A<sup>1</sup> are not both N. In certain preferred embodiments of this aspect of the invention, Z

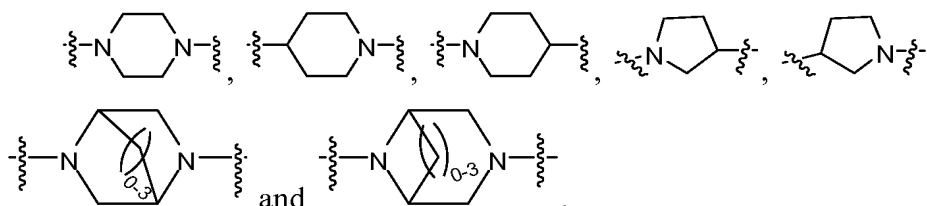
includes a 0 to 3 carbon bridge between non-adjacent carbon ring atoms. Preferred embodiments of Z in this aspect of the invention are



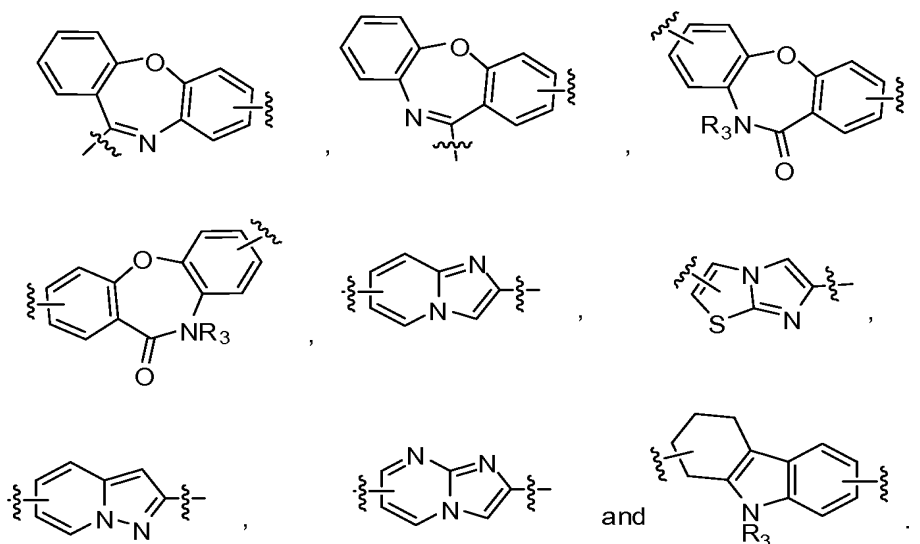
**[0193]** In another aspect, the invention comprises compounds according to the previous embodiments in which Z is



**[0194]** wherein A and A<sup>1</sup> are independently CR<sup>11</sup> or N, wherein R<sup>11</sup> is -OH, alkyl, alkenyl, alkynyl or aryl, n<sub>1</sub> and n<sub>2</sub> are each independently 0-3, and R is R<sup>20</sup>-X<sup>50</sup>-, wherein R<sup>20</sup> is aryl, -alkyl-aryl, heteroaryl, -alkyl-heteroaryl, cycloalkyl, -alkyl-cycloalkyl, -alkyl-heterocyclyl or heterocyclyl and X<sup>50</sup> is C<sub>0</sub>-C<sub>3</sub>-alkyl-X<sup>51</sup>-C<sub>0</sub>-C<sub>3</sub>alkyl, wherein X<sup>51</sup> selected from the group consisting of -SO<sub>2</sub>-, -NH-SO<sub>2</sub>-, -C(O)-, -NH-C(O)-, -O-C(O)-, -C(S)-, -NH-C(S)-, -O-C(S)-, -NH-C(O)-NH-, -O-C(O)-NH- and -NH-C(O)-O, provided that when n<sub>1</sub> and n<sub>2</sub> are 0, then A and A<sup>1</sup> are not both N. In certain preferred embodiments of this aspect of the invention, Z includes a 0 to 3 carbon bridge between non-adjacent carbon ring atoms. Preferred embodiments of Z in this aspect of the invention are



**[0195]** In another aspect, the invention comprises compounds according to the previous embodiments, wherein Z is selected from the group consisting of



[0196] Preferably, in embodiment (I):

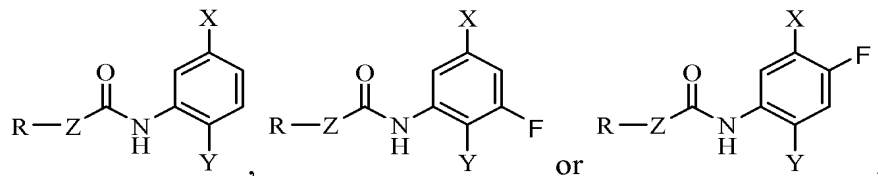
[0197] X is thienyl (preferably thien-2-yl), pyridyl (preferably pyrid-3-yl or 4-yl), or phenyl, each optionally substituted as described for embodiment (I), and/or

[0198] R is morpholinyl, pyrrolidinyl, 2,5-diazabicyclo[2.2.1]heptane, azetidine, piperidinyl, or piperazinyl (preferably piperazin-4-yl), each of which is optionally substituted with hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl, C<sub>5</sub>-C<sub>6</sub>-cycloalkyl, or NR<sup>7</sup>R<sup>8</sup>-C<sub>0</sub>-C<sub>3</sub>-alkyl.

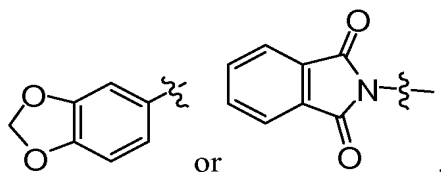
[0199] Preferably, in embodiment (I):

[0200] -Z-R is -phenyl-heterocyclyl, optionally oxo substituted.

[0201] In a preferred embodiment of the present invention, Formula I has a generic structure

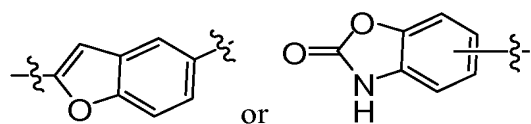


[0202] Preferably in embodiment (IV), R is



[0203] Preferably in embodiment (IV), Z is

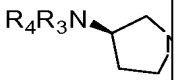
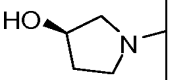
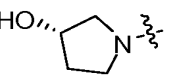
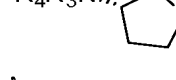
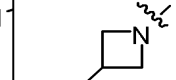

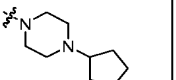

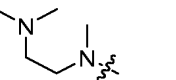
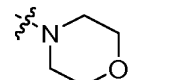
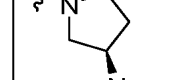
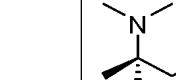
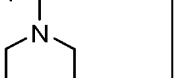
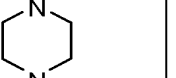




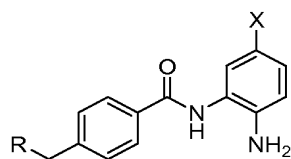
[0204] In a preferred embodiment of the compounds according to the present invention, X is selected from the group consisting of

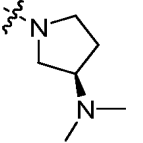

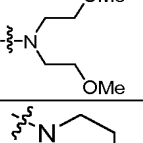

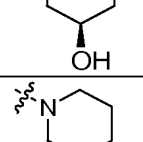

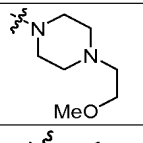

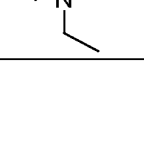



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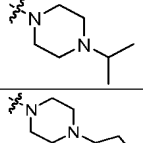

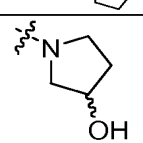

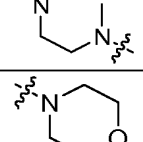

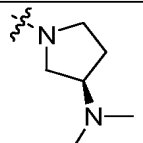





[0205] and/or R is selected from the group consisting of

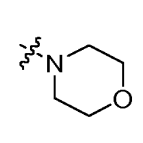

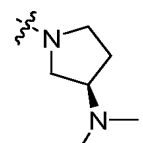

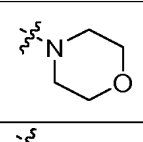

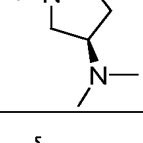

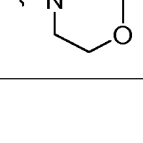


					
					
					

[0206] Preferred compounds according to embodiment (I) include those for formula I<sub>1</sub>:



Cpd	R	X
9		
10		
11		
12		
13		
14		

Cpd	R	X
15		
16		
17		
18		
19		
20		

Cpd	R	X
21		
22		
23		
24		
25		

Cpd	R	X
26		
27		
28		
29		

Cpd	R	X
31		
32		
540		

Cpd	R	X

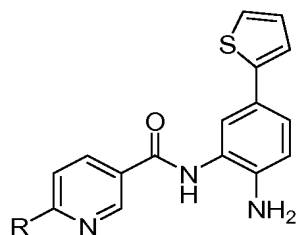
[0207] Preferably in embodiment (II):

[0208] X is thien-2-yl;

[0209] Z is pyrid-3-yl; and

[0210] R is pyrrolidinyl (preferably pyrrolidin-1-yl), piperidinyl (preferably piperidin-1-yl), or piperazinyl (preferably piperazin-1-yl), each optionally substituted with C<sub>1</sub>-C<sub>3</sub>-alkyl, dialkylamino (preferably dimethylamino) or morpholino.

[0211] Preferred compounds according to embodiment (II) include those of formula I<sub>II</sub>:



Cpd	R
49	
50	
51	
253	

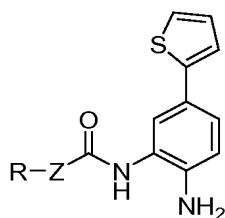
[0212] Preferably in embodiment (III)

[0213] X is thien-2-yl;

[0214] Z is phenyl or pyridin-2-yl, and

[0215] R is thienyl (preferably thien-2-yl), 1*H*-pyrazolyl (preferably 1*H*-pyrazol-4-yl), or phenyl optionally substituted with from 1 to 3 C<sub>1</sub>-C<sub>3</sub>-alkoxy (preferably methoxy).

[0216] Preferred compounds according to embodiment (III) include those of formula I<sub>III</sub>:



Cpd	R-Z	X
56		
57		
58		
499		
531		

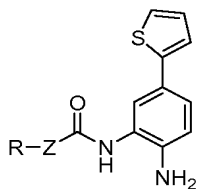
[0217] Preferably in embodiment (IV):

[0218] X is thien-2-yl;

[0219] Z is phenyl, thienyl (preferably thien-2-yl), pyridyl (preferably pyrid-2-yl, -3-yl or -4-yl), furyl (preferably furan-2-yl), and

[0220] R is pyridyl (preferably pyridine-2-yl), pyrrolidinyl-C<sub>0</sub>-C<sub>2</sub>-alkyl (pyrrolidine-2-ylethyl), morpholino-C<sub>0</sub>-C<sub>1</sub>-alkyl, pyrrolyl (preferably pyrrol-1-yl), pyrazolyl (preferably pyrazol-1-yl), halo, or cyano;

[0221] Preferred compounds according to embodiment (IV) include those of formula I<sub>IVa</sub>:

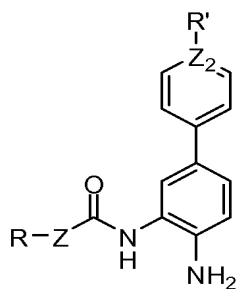


Cpd	R-Z
61	
62	
63	
64	

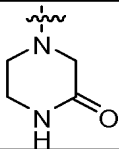
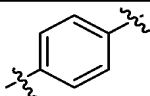
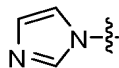
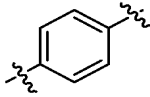
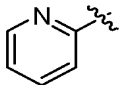
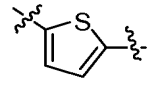
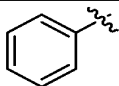
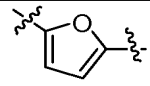
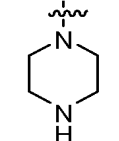
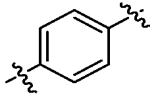
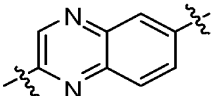
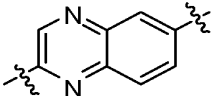
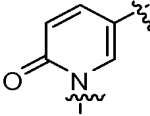
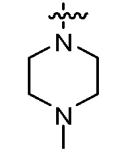
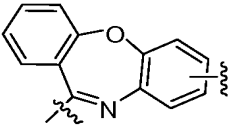
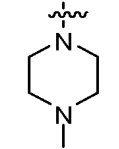
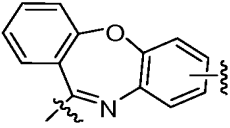
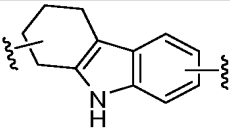
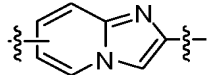
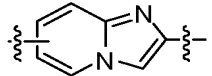
Cpd	R-Z
65	
67	
68	
69	
70	

Cpd	R-Z
71	
72	
488	

[0222] Preferred compounds according to embodiment (IV) include those of formula I<sub>IVb</sub>



Cpd	R	Z	Z <sub>2</sub>	R'
529			C	H

Cpd	R	Z	Z <sub>2</sub>	R'
484			C	H
491			C	H
498			C	F
494			C	F
476			C	H
464	H		N	-
465	H		C	H
539	Bn		C	F
552			N	-
551			C	H
544	H		C	H
	H		C	H
	H		N	-

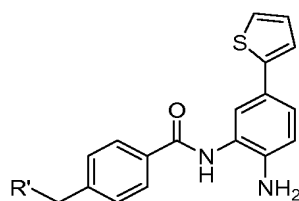
Cpd	R	Z	Z <sub>2</sub>	R'
	H		C	H
	H		N	-
	H		C	H
	H		C	F
	H		N	-
	H		C	H
	MeO-		C	H
			C	H
538	HOCH <sub>2</sub> -		C	H
463	MeO-		N <sup>+</sup>	-O <sup>-</sup>
			C	H
			C	F

[0223] Preferably in embodiment (V):

[0224] X is thienyl-2-yl; and

[0225] R is -(CH<sub>2</sub>)-(piperidiny, piperaziny, or pyrrolidiny), optionally substituted as described for embodiment (V), above.

[0226] Preferred compounds according to embodiment (V) include those of formula IV:



Cpd	R'
76	
77	
78	
79	

Cpd	R'
80	
81	
82	
83	
84	
85	

Cpd	R'
86	
87	
88	
89	
90	
91	

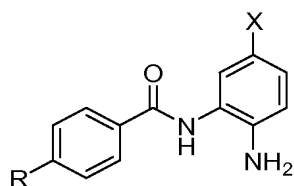
Cpd	R'
92	
222	

[0227] Preferably in embodiment (VI):

[0228] X is thienyl-2-yl optionally substituted with halo; and

[0229] R is piperidinyl (preferably piperidin-1-yl), piperazinyl, or pyrrolidinyl, each optionally substituted with the optional substituents described for the heterocyclyl in the definition of R<sup>3</sup> and R<sup>4</sup> in embodiment (VI), above.

[0230] Preferred compounds according to embodiment (VI) include those of formula I<sub>VI</sub>:





Cpd	R	X
101		
102		
103		
104		

Cpd	R	X
105		
106		
107		
108		

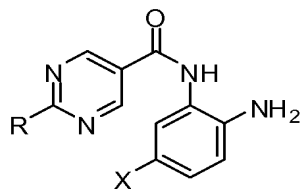
Cpd	R	X
109		
110		
249		
271		

[0231] Preferably in embodiment (VII):

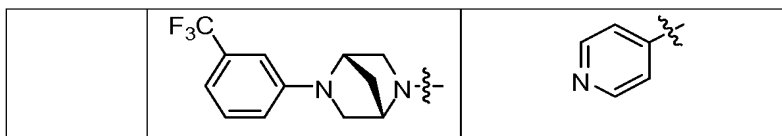
[0232] X is thiophen-2-yl;

[0233] R is morpholino-, or piperidinyl or piperazinyl each optionally substituted with the substituents of the heterocyclyl in the definition of R<sup>3</sup> and R<sup>4</sup> in embodiment (VII).

[0234] Preferred compounds of embodiment (VII) include those of formula I<sub>VII</sub>:



	R	X
124		
125		
126		
127		



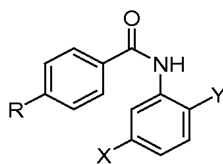
[0235] Preferably in embodiment (VIII):

[0236] X is thienyl (preferably thien-2-yl), phenyl, pyrrolyl (preferably pyrrol-2-yl), or 1*H*-pyrazolyl (preferably 1*H*-pyrazol-4-yl), each optionally substituted with amino;

[0237] Y is amino or F; and

[0238] R is methoxy or pyridyl (preferably pyridin-1-yl).

[0239] Preferred compounds according to embodiment (VIII) include those of formula I<sub>VIII</sub>:



Cpd	R	X	Y
147	CH <sub>3</sub> O-		NH <sub>2</sub>
148			NH <sub>2</sub>
149			NH <sub>2</sub>

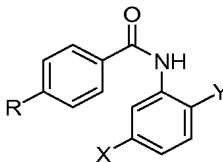
Cpd	R	X	Y
150			NH <sub>2</sub>
456	CH <sub>3</sub> O-		-NHSO <sub>2</sub> NH <sub>2</sub>

[0240] Preferably in embodiment (IX):

[0241] X is thienyl (preferably thien-2-yl), phenyl, pyridyl (preferably pyridine-2-yl), or furyl, each of which is optionally substituted with halo; and

[0242] R is pyridyl (preferably pyridine-2-yl), piperidinyl optionally N-substituted with methyl, or morpholinomethyl.

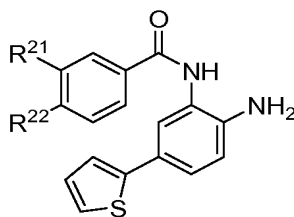
[0243] Preferred compounds according to embodiment (IX) include those of formula I<sub>IX</sub>:



Cpd	R	X	Y
170			NH <sub>2</sub>
171			NH <sub>2</sub>
173			NH <sub>2</sub>
174			NH <sub>2</sub>
175			NH <sub>2</sub>

Cpd	R	X	Y
176			NH <sub>2</sub>
177			NH <sub>2</sub>
178			NH <sub>2</sub>
179			NH <sub>2</sub>

[0244] Preferred compounds of embodiment (X) include those of formula I<sub>X</sub>:

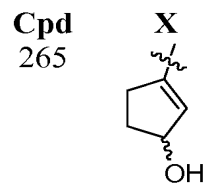
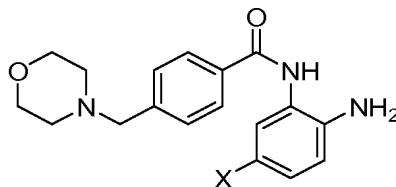


Cpd	R <sup>21</sup>	R <sup>22</sup>
140	-OH	Ac-NH-
232		H

Cpd	R <sup>21</sup>	R <sup>22</sup>
233	H	
234	H	
235	H	

Cpd	R <sup>21</sup>	R <sup>22</sup>
300	OH	H

[0245] Preferred compounds of embodiment (XI) include those of formula I<sub>XI</sub>:



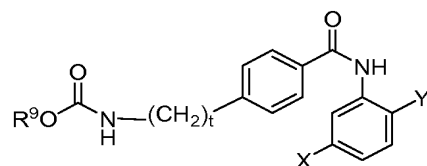
[0246] Preferably in embodiment (XII):

[0247] X is thienyl (preferably thien-2 or 3-yl), phenyl, pyridyl (preferably pyridine-2-yl) optionally substituted with 1 or 2 halo;

[0248] Y is  $-NH_2$ ; and

[0249]  $R^{10}$  is  $-N(C_1-C_3\text{-alkyl})(C_1-C_3\text{-alkyl})$  (preferably dimethylamino);

[0250] Preferred compounds according to embodiment (XII) are those of formula I<sub>XII</sub>:



Cpd	R <sup>9</sup>	t	X	Y
221		1		NH <sub>2</sub>
283		0		NH <sub>2</sub>
284		0		NH <sub>2</sub>
285		0		NH <sub>2</sub>
286		0		NH <sub>2</sub>
287		0		NH <sub>2</sub>
288		0		NH <sub>2</sub>
289		0		NH <sub>2</sub>
290		0		NH <sub>2</sub>
291		0		NH <sub>2</sub>

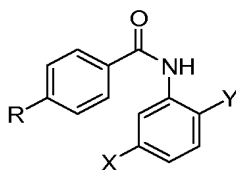
Cpd	R <sup>9</sup>	t	X	Y
292		0		NH <sub>2</sub>
293		0		NH <sub>2</sub>
294		0		NH <sub>2</sub>
295		0		NH <sub>2</sub>
296		0		OH
541		1		NH <sub>2</sub>
		0		NH <sub>2</sub>

[0251] Preferably in embodiment (XIII):

[0252] X is thienyl (preferably thien-2-yl), pyridyl (preferably pyridine-2-yl), 3-oxo-cyclopent-1-yl, or phenyl, each of which is optionally substituted with 1 or two halo; and

[0253] Y is  $-\text{NH}_2$  or  $-\text{OH}$ .

[0254] Preferred compounds of embodiment (XIII) include those of formula I<sub>XIII</sub>:



Cpd	R	X	Y
261	OAc		$\text{NH}_2$
262	OH		$\text{NH}_2$
301	OAc		$\text{NH}_2$
302	OH		$\text{NH}_2$
303	OH		$\text{NH}_2$
304	OAc		$\text{NH}_2$
305	OH		$\text{NH}_2$

Cpd	R	X	Y
306	OAc		$\text{NH}_2$
307	OH		$\text{NH}_2$
308	OH		$\text{NH}_2$
309	OH		$\text{NH}_2$
310	OH		OH

[0255] Preferably in embodiment (XIV):

[0256] R is  $\text{R}^{20}-\text{C}(\text{O})$ -ethyl or  $\text{R}^{20}-\text{C}(\text{O})$ -ethenyl.

[0257] Preferred compounds of embodiment (XIV) include those of formula I, wherein:

Cpd	R
226	$\text{HO}-\text{C}(\text{O})-\text{CH}=\text{CH}-$
227	$\text{HO}-\text{NH}-\text{C}(\text{O})-\text{CH}=\text{CH}-$
230	$\text{MeO}-\text{C}(\text{O})-\text{CH}_2-\text{CH}_2-$
231	$\text{HO}-\text{C}(\text{O})-\text{CH}_2-\text{CH}_2-$

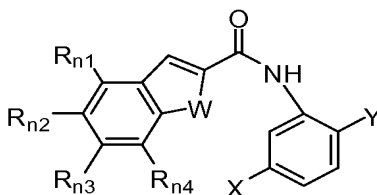
[0258] Preferably in embodiment (XVI) X is phenyl or pyridyl, each of which is optionally substituted.

[0259] Preferably in embodiment (XVI) X is optionally substituted with one or two halogen, preferably F.

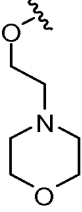
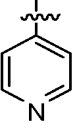
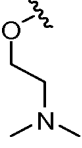
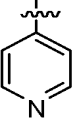
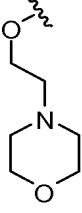
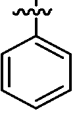
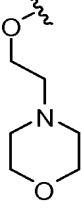
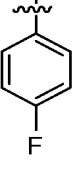
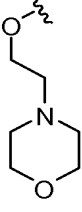
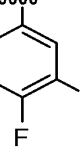
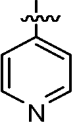
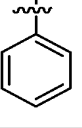
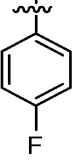
[0260] Preferably in embodiment (XVI) R is H, alkoxy,  $-O-(CH_2)_{2-3}$ -heterocycle or  $-O-(CH_2)_{2-3}-N(R^3)(R^4)$ , wherein preferably the heterocycle moiety is morpholine or piperidine.

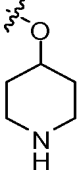
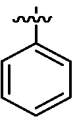
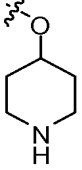
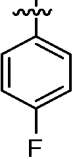
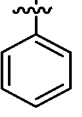
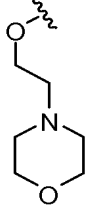
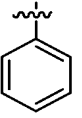
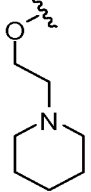
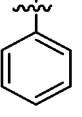
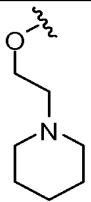
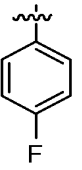
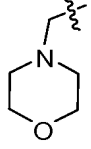
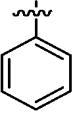
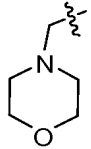
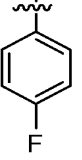
[0261] In a preferred embodiment of the compounds according to Formula (I), X is optionally substituted with one, two or three substituents independently selected from the group consisting of halo, oxo, hydroxy,  $C_1$ - $C_3$ -hydrocarbyl, methoxy,  $HalCH_2-O-$ ,  $Hal_2CH-O-$ ,  $Hal_3C-O-$  (preferably  $F_3C-O-$ ),  $NH_2-$ ,  $-N(C_1-C_3alkyl)_2$ ,  $-CN$ ,  $-S(O)_{0-2}-C_1-C_4alkyl$ ,  $-CF_3$ , and mono-, di-, or tri- halo substituted alkyl, or, when there are two optional substituents bonded to adjacent atoms of the phenyl, thienyl, or pyridyl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heteroalkyl having 1, 2, or 3 annular heteroatoms.

[0262] Preferred compounds of embodiment (XVI) include those of formula I<sub>x</sub>:

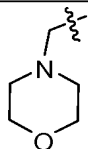
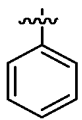
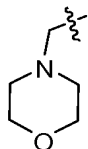
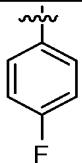
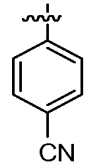
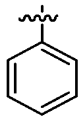


Cpd	R <sub>n1</sub>	R <sub>n2</sub>	R <sub>n3</sub>	R <sub>n4</sub>	W	X	Y
378	-OMe	-H	-OMe	-H	O		-NH <sub>2</sub>
398	-H	-H		-H	O		-NH <sub>2</sub>

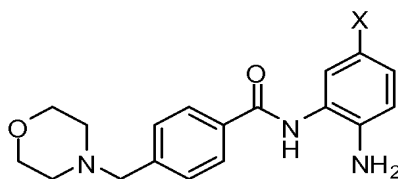
Cpd	R <sub>n1</sub>	R <sub>n2</sub>	R <sub>n3</sub>	R <sub>n4</sub>	W	X	Y
466	-H	-H		-H	O		-NH <sub>2</sub>
467	-H	-H		-H	O		-NH <sub>2</sub>
468	-H	-H		-H	{		-NH <sub>2</sub>
469	-H	-H		-H	O		-NH <sub>2</sub>
470	-H	-H		-H	O		-NH <sub>2</sub>
471	-H	-OMe	-OMe	-H	O		-NH <sub>2</sub>
472	-H	-OMe	-OMe	-H	O		-NH <sub>2</sub>
473	-H	-OMe	-OMe	-H	O		-NH <sub>2</sub>

Cpd	R <sub>n1</sub>	R <sub>n2</sub>	R <sub>n3</sub>	R <sub>n4</sub>	W	X	Y
491	H	H		H	O		-NH <sub>2</sub>
553	H	H		H	O		-NH <sub>2</sub>
	-H	-OMe	-OMe	-H	S		-NH <sub>2</sub>
	H		H	H	O		-NH <sub>2</sub>
	H		H	H	O		-NH <sub>2</sub>
	H		H	H	O		-NH <sub>2</sub>
	H	-OMe	H		O		-NH <sub>2</sub>
	H	-OMe	H		O		-NH <sub>2</sub>

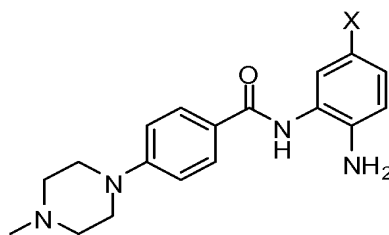


Cpd	R <sub>n1</sub>	R <sub>n2</sub>	R <sub>n3</sub>	R <sub>n4</sub>	W	X	Y
	H		H	-OMe	O		-NH <sub>2</sub>
	H		H	-OMe	O		-NH <sub>2</sub>
	H		H	H	O		-NH <sub>2</sub>

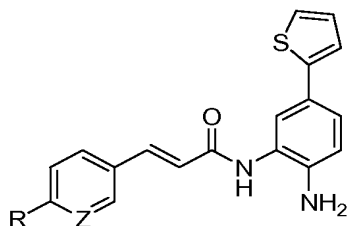
[0263] Other preferred compounds of embodiment (XVI) include those of formula I<sub>XI</sub>, where in X is aryl, -aryl-heteroaryl, heteroaryl-aryl, heterocyclyl or heteroaryl, wherein said aryl or heteroaryl is optionally substituted with one to three alkyl, halo, CN, alkyloxy, alkyl-OH, -OH, alkyl-NH<sub>2</sub>, -N(alkyl)<sub>2</sub>, alkyl-O-alkyl, -S(O)<sub>0-2</sub>alkyl, -C<sub>0</sub>-C<sub>3</sub>alkyl-NR<sub>3</sub>C(O)alkyl, -C(O)NR<sub>3</sub>alkyl, -alkyl-CN, CF<sub>3</sub>, -O-CF<sub>3</sub>, -C<sub>0</sub>-C<sub>3</sub>alkyl-C(O)OR<sub>3</sub>, -C<sub>0</sub>-C<sub>3</sub>alkyl-NR<sub>3</sub>C(O)Oalkyl, -C(O)Oalkyl, -S(O)<sub>2</sub>NHalkyl or -S(O)<sub>2</sub>NH<sub>2</sub>:

I<sub>XI</sub>

[0264] Other preferred compounds of embodiment (XVI) include those of formula I<sub>XII</sub>, where in X is aryl, -aryl-heteroaryl, heterocyclyl, heteroaryl-aryl or heteroaryl, wherein said aryl or heteroaryl is optionally substituted with one to three alkyl, halo, CN, alkyloxy, alkyl-OH, -OH, alkyl-NH<sub>2</sub>, -N(alkyl)<sub>2</sub>, alkyl-O-alkyl, -S(O)<sub>0-2</sub>alkyl, -C<sub>0</sub>-C<sub>3</sub>alkyl-NR<sub>3</sub>C(O)alkyl, -C(O)NR<sub>3</sub>alkyl, -alkyl-CN, CF<sub>3</sub>, -O-CF<sub>3</sub>, -C<sub>0</sub>-C<sub>3</sub>alkyl-C(O)OR<sub>3</sub>, -C<sub>0</sub>-C<sub>3</sub>alkyl-NR<sub>3</sub>C(O)Oalkyl, -C(O)Oalkyl, -S(O)<sub>2</sub>NHalkyl or -S(O)<sub>2</sub>NH<sub>2</sub>:

I<sub>XII</sub>

[0265] In another aspect, the invention comprises compounds of formula II:



[0266] and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complex thereof, and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

[0267] Z is N or CH;

[0268] R is -CH<sub>2</sub>OR<sup>3</sup>, -C<sub>0</sub>-C<sub>3</sub>alkyl-N(R<sup>3</sup>)-C<sub>0</sub>-C<sub>3</sub>alkyl-heteroaryl, -C<sub>0</sub>-C<sub>3</sub>alkyl-N(R<sup>3</sup>)-C<sub>0</sub>-C<sub>3</sub>alkyl-aryl, -(CH<sub>2</sub>)<sub>m</sub>-aryl, -(CH<sub>2</sub>)<sub>m</sub>-heteroaryl or (5- or 6-membered heteroaryl)-(CH<sub>2</sub>)<sub>m</sub>-, wherein the aryl and heteroaryl rings are optionally substituted with 1, 2, or 3 methoxy;




[0269] m is 0 or 1;

[0270] wherein R<sup>3</sup> is as defined in embodiment (I) above.

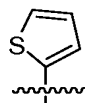
[0271] Preferably, compounds of formula II are those in which R is pyridyl (preferably pyridine-2-yl), phenyl, or morpholino.

[0272] Preferred compounds for formula II include the following:

Cpd	Z	m	R
42	N	0	
43	N	0	

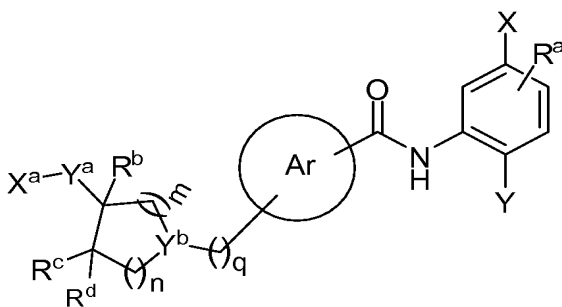
Cpd	Z	m	R
44	N	0	
96	CH	1	
166	N	1	
	CH	0	-CH <sub>2</sub> OH

[0273] In a preferred embodiment of the compounds according to Formula (II), the



moiety is optionally substituted with one, two or three substituents independently selected from the group consisting of halo, oxo, hydroxy, C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl, methoxy, HalCH<sub>2</sub>-O-, Hal<sub>2</sub>CH-O-, Hal<sub>3</sub>C-O- (preferably F<sub>3</sub>C-O-), NH<sub>2</sub>-, -N(C<sub>1</sub>-C<sub>3</sub>alkyl)<sub>2</sub>-, -CN, -S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>4</sub>alkyl, -CF<sub>3</sub>, and mono-, di-, or tri- halo substituted alkyl, or, when there are two optional substituents bonded to adjacent atoms of the phenyl, thienyl, or pyridyl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heteroalkyl having 1, 2, or 3 annular heteroatoms.

[0274] In another aspect, the invention comprises compounds of formula III



(III)

and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof, and racemic and scalemic mixtures, diastereomers and enantiomers thereof wherein

[0275] X is aryl, cycloalkyl, heteroaryl or heterocyclyl, each of which is optionally substituted;

[0276] Ar is aryl, heteroaryl, cycloalkyl or heterocyclyl, each of which is optionally substituted;

[0277] R<sup>a</sup> is H or halo;

[0278]  $R^b$ ,  $R^c$  and  $R^d$  are each independently hydrogen,  $C_1$ - $C_8$  alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl or halo; or

[0279]  $R^b$  and  $R^c$  together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heteroalkyl having 1 or 2 annular heteroatoms; each of which is optionally substituted with from 1 to 3 substituents;

[0280] Y is  $-NH_2$  or  $-OH$ ;

[0281]  $Y^b$  is  $-N-$  or  $-CH-$ ;

[0282]  $Y^a$  is direct bond,  $-O-$ ,  $-N(R^{34})-$ ,  $-C(O)-$ ,  $-OC(O)-$ ,  $-C(O)O-$ ,  $-N(R^{34})-C(O)-$ ,  $-C(O)-N(R^{34})-$ ,  $-N(R^{34})-C(S)-$ ,  $-C(S)-N(R^{34})-$ ,  $-N(R^{34})-C(O)-N(R^{35})-$ ,  $-N(R^{34})-C(NR^{34})-N(R^{35})-$ ,  $-N(R^{34})-C(NR^{35})-$ ,  $-C(NR^{35})-N(R^{34})-$ ,  $-N(R^{34})-C(S)-N(R^{35})-$ ,  $-N(R^{34})-C(O)-O-$ ,  $-O-C(O)-N(R^{34})-$ ,  $-N(R^{34})-C(S)O-$ ,  $-O-C(S)-N(R^{35})-$ ,  $-S(O)_{0-2}-$ ,  $-SO_2N(R^{35})-$ ,  $-N(R^{35})-SO_2-$ ,  $N(R^{34})-S(O)_2-N(R^{35})-$ ,  $-O-C_1-C_3alkyl-$ ,  $-N(R^{34})-C_1-C_3alkyl-$ ,  $-C(O)-C_1-C_3alkyl-$  or  $-O-C(O)-C_1-C_3alkyl-$ ;

[0283]  $X^a$  is  $C_1$ - $C_8alkyl-$ ,  $C_1$ - $C_8alkenyl-$ ,  $C_1$ - $C_8alkynyl-$ ,  $C_0$ - $C_3alkyl-C_1$ - $C_8alkenyl-C_0$ - $C_3alkyl-$ ,  $C_0$ - $C_3alkyl-C_1$ - $C_8alkynyl-C_0$ - $C_3alkyl-$ ,  $C_1$ - $C_3alkyl-O-C_1$ - $C_3alkyl-$ ,  $HO-C_1$ - $C_3alkyl-$ ,  $C_1$ - $C_4alkyl-N(R^{34})-C_0$ - $C_3alkyl-$ ,  $N(R^{34})(R^{35})-C_0$ - $C_3alkyl-$ ,  $C_1$ - $C_3alkyl-S(O)_{0-2}-C_1$ - $C_3alkyl-$ ,  $CF_3-C_0$ - $C_3alkyl-$ ,  $CF_2H-C_0$ - $C_3alkyl-$ ,  $C_1$ - $C_8heteroalkyl-$ , aryl, cycloalkyl, heterocyclyl, heteroaryl, aryl- $C_1$ - $C_3alkyl-$ , cycloalkyl- $C_1$ - $C_3alkyl-$ , heterocyclyl- $C_1$ - $C_3alkyl-$ , heteroaryl- $C_1$ - $C_3alkyl-$ , aryl- $C_0$ - $C_2alkyl-heterocyclyl-C_0$ - $C_2alkyl-$ , heteroaryl- $C_0$ - $C_2alkyl-heterocyclyl-C_0$ - $C_2alkyl-$ ,  $N(R^{34})(R^{35})-heterocyclyl-C_0$ - $C_3alkyl-$ , heteroaryl- $C_0$ - $C_3alkyl-heterocyclyl-$  or  $C_1$ - $C_4alkyl-CH(N(R^{34})(R^{35}))-C(O)-N(R^{34})-aryl-$ , wherein the aryl, cycloalkyl, heteroaryl and heterocycyl are optionally substituted with from 1 to 3 independently selected substituents;

or

[0284]  $X^a-Y^a-$  is selected from the group consisting of  $H-$ , halo-,  $HO-$ ,  $HS-$ ,  $HC(O)-$ ,  $HOC(O)-$ ,  $C_1$ - $C_4alkyl-$ ,  $H_2N-$ ,  $(R^{34})(R^{35})N-$ ,  $C_1$ - $C_4alkyl-NH-$ ,  $(C_1-C_4alkyl)_2-N-$ ,  $HC(O)N(R^{34})-$ ,  $(R^{34})(R^{35})N-S(O)_2-N(R^{36})-$ ,  $(R^{34})(R^{35})N-C(O)-$ ,  $H_2N-C(O)-$ ,  $HC(S)N(R^{34})-$ ,  $(R^{34})(R^{35})N-C(S)-$ ,  $H_2N-C(S)-$ ,  $(R^{34})(R^{35})N-C(O)-O-$ ,  $(R^{34})(R^{35})N-C(S)-O-$ ,  $(R^{34})(R^{35})N-C(O)-N(R^{36})-$ ,  $(C_1-C_3alkylN)_2-C=N-$ ,  $(R^{34})(R^{35})N-C(NR^{37})-N(R^{36})-$ ,  $(R^{34})(R^{35})N-C(NR^{36})-$ , cycloalkyl- $C_0$ - $C_2alkyl-C(NR^{36})-$ ,

heterocyclyl-C<sub>0</sub>-C<sub>2</sub>alkyl-C(NR<sup>36</sup>)-, aryl-C<sub>0</sub>-C<sub>2</sub>alkyl-C(NR<sup>36</sup>)-,  
 heteroaryl-C<sub>0</sub>-C<sub>2</sub>alkyl-C(NR<sup>36</sup>)-, C<sub>0</sub>-C<sub>3</sub>alkyl-C(NR<sup>36</sup>)-, C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-N(R<sup>36</sup>)-,  
 CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-N(R<sup>36</sup>)-, CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(R<sup>36</sup>)-,  
 aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-N(R<sup>36</sup>)-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-N(R<sup>36</sup>)-,  
 cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-N(R<sup>36</sup>)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-N(R<sup>36</sup>)-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-O-C(O)-NH-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-C<sub>1</sub>-C<sub>4</sub>alkyl-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-NH-C(O)-O-, C<sub>1</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-, Me-C(O)-O-, Me-C(O)-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-,  
 aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(C<sub>1</sub>-C<sub>4</sub>alkyl)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-,  
 heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(C<sub>1</sub>-C<sub>4</sub>alkyl)-,  
 heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-,  
 heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-,  
 heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(C<sub>1</sub>-C<sub>4</sub>alkyl)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-,  
 cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(C<sub>1</sub>-C<sub>4</sub>alkyl)-,  
 cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-,  
 cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-,  
 aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-,  
 aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-,  
 heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-,  
 heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-,  
 heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-,  
 cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-,  
 cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-,  
 heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-,  
 heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-,  
 heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-,  
 cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-,  
 cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-,  
 cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-,  
 aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-NH-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-,

heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>1</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-O-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-,  
 HO-C<sub>1</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, HO-C<sub>1</sub>-C<sub>4</sub>alkyl-N(H)-, HO-C<sub>1</sub>-C<sub>4</sub>alkyl-N(R<sup>3</sup>)-,  
 HO-C<sub>1</sub>-C<sub>4</sub>alkyl-O-, HO-C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-, HO-C<sub>2</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-,  
 HO-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, HO-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>1</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)C(S)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-,  
 HO-C<sub>2</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-, HO-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-,  
 HO-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-, (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>1</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-,  
 (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>1</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>1</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-,  
 (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>1</sub>-C<sub>4</sub>alkyl-C(O)-O-, (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-,  
 (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>2</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-,  
 (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(NH)-N(H)-, (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-,  
 (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-, (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-,  
 (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-O-, (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-,  
 (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-,  
 (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>1</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-, (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-,  
 (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-, (C<sub>1</sub>-C<sub>4</sub>alkyl)-O-C(O)C<sub>1</sub>-C<sub>8</sub>alkyl-C(O)-(H)-,  
 HO-C(O)C<sub>1</sub>-C<sub>8</sub>alkyl-C(O)-N(H)-, HO-NH-C(O)C<sub>1</sub>-C<sub>8</sub>alkyl-C(O)-N(H)-,  
 CF<sub>2</sub>H-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-,  
 CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-N(R<sup>3</sup>)-, CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-O-, CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-,  
 CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-, CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)C(O)-N(H)-,  
 CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-, CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-,  
 CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-, CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-,  
 CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-, CF<sub>2</sub>H-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-, CF<sub>2</sub>H-C<sub>0</sub>-C<sub>4</sub>alkyl-O-,  
 CF<sub>2</sub>H-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-, CF<sub>2</sub>H-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-,  
 CF<sub>2</sub>H-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)C(O)-N(H)-, CF<sub>2</sub>H-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-,  
 CF<sub>2</sub>H-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-, CF<sub>2</sub>H-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-,  
 CF<sub>2</sub>H-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-, CF<sub>2</sub>H-C<sub>0</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-, (H)(R<sup>34</sup>)N-C<sub>1</sub>-C<sub>3</sub>alkyl-,

(H)(R<sup>34</sup>)N-C<sub>1</sub>-C<sub>3</sub>alkyl-, HO-C<sub>1</sub>-C<sub>3</sub>alkyl-, (H)(R<sup>34</sup>)N-S(O)<sub>2</sub>-N(R<sup>35</sup>)-, (H)(R<sup>35</sup>)N-S(O)<sub>2</sub>-, (H)(R<sup>34</sup>)N-C(S)-O-, (H)(R<sup>34</sup>)N-C(O)-O-, (H)(R<sup>34</sup>)N-C(S)-N(R<sup>35</sup>)-, (H)(R<sup>34</sup>)N-C(NR<sup>35</sup>)-, (H)(R<sup>34</sup>)N-C(NR<sup>34</sup>)-N(R<sup>38</sup>)-, (H)(R<sup>34</sup>)N-C(O)-N(R<sup>35</sup>)-, HO-C(O)-C<sub>1</sub>-C<sub>3</sub>alkyl-, C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-NH- and ((R<sup>34</sup>)(R<sup>35</sup>)N)<sub>2</sub>-C=N-;

**[0285]** m and n are independently 0, 1, 2 or 3;

**[0286]** q is 0, 1 or 2;

**[0287]** R<sup>34</sup>, R<sup>35</sup>, R<sup>36</sup> and R<sup>37</sup> are each independently selected from the group consisting of hydrogen, cyano, oxo, hydroxyl, -C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>1</sub>-C<sub>8</sub>heteroalkyl, C<sub>1</sub>-C<sub>8</sub>alkenyl, carboxamido, C<sub>1</sub>-C<sub>3</sub>alkyl-carboxamido-, carboxamido-C<sub>1</sub>-C<sub>3</sub>alkyl-, amidino, C<sub>2</sub>-C<sub>8</sub>hydroxyalkyl, C<sub>1</sub>-C<sub>3</sub>alkylaryl-, aryl-C<sub>1</sub>-C<sub>3</sub>alkyl-, C<sub>1</sub>-C<sub>3</sub>alkylheteroaryl-, heteroaryl-C<sub>1</sub>-C<sub>3</sub>alkyl-, C<sub>1</sub>-C<sub>3</sub>alkylheterocyclyl-, heterocyclyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, C<sub>1</sub>-C<sub>3</sub>alkylcycloalkyl-, cycloalkyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, C<sub>2</sub>-C<sub>8</sub>alkoxy-, C<sub>2</sub>-C<sub>8</sub>alkoxy-C<sub>1</sub>-C<sub>4</sub>alkyl-, C<sub>1</sub>-C<sub>8</sub>alkoxycarbonyl-, aryloxy carbonyl-, aryl-C<sub>1</sub>-C<sub>3</sub>alkoxycarbonyl-, heteroaryloxy carbonyl-, heteroaryl-C<sub>1</sub>-C<sub>3</sub>alkoxycarbonyl-, C<sub>1</sub>-C<sub>8</sub>acyl, C<sub>0</sub>-C<sub>8</sub>alkyl-carbonyl-, aryl-C<sub>0</sub>-C<sub>8</sub>alkyl-carbonyl-, heteroaryl-C<sub>0</sub>-C<sub>8</sub>alkyl-carbonyl-, cycloalkyl-C<sub>0</sub>-C<sub>8</sub>alkyl-carbonyl-, C<sub>0</sub>-C<sub>8</sub>alkyl-N(H)-carbonyl-, aryl-C<sub>0</sub>-C<sub>8</sub>alkyl-N(H)-carbonyl-, heteroaryl-C<sub>0</sub>-C<sub>8</sub>alkyl-N(H)-carbonyl-, cycloalkyl-C<sub>0</sub>-C<sub>8</sub>alkyl-N(H)-carbonyl-, C<sub>0</sub>-C<sub>8</sub>alkyl-O-carbonyl-, aryl-C<sub>0</sub>-C<sub>8</sub>alkyl-O-carbonyl-, heteroaryl-C<sub>0</sub>-C<sub>8</sub>alkyl-O-carbonyl-, cycloalkyl-C<sub>0</sub>-C<sub>8</sub>alkyl-O-carbonyl-, C<sub>1</sub>-C<sub>8</sub> alkylsulfonyl-, arylalkylsulfonyl-, arylsulfonyl-, heteroarylalkylsulfonyl-, heteroarylsulfonyl-, C<sub>1</sub>-C<sub>8</sub>alkyl-N(H)-sulfonyl-, arylalkyl-N(H)-sulfonyl-, aryl-N(H)-sulfonyl-, heteroarylalkyl-N(H)-sulfonyl-, heteroaryl-N(H)-sulfonyl, aroyl, aryl, cycloalkyl, heterocyclyl, heteroaryl, aryl-C<sub>1</sub>-C<sub>3</sub>alkyl-, cycloalkyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, heterocyclyl-C<sub>1</sub>-C<sub>3</sub> alkyl-, heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl-, and a protecting group, wherein each of the foregoing is further optionally substituted with one more moieties; or

**[0288]** R<sup>34</sup> and R<sup>35</sup> taken together with the N to which they are attached form a heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents, wherein the heterocyclyl may also be bridged (forming a bicyclic moiety with a methylene, ethylene or propylene bridge),

[0289] provided that 1) when  $Y^b$  is N, then m is not 0 if  $Y^a$  is bound to the ring comprising Y, via a N, S or O in  $Y^a$ , or 2) when m and n are both 0 then  $Y^b$  is -CH-.

[0290] In a preferred embodiment of the compounds according to Formula (III), X is optionally substituted with one, two or three substituents independently selected from the group consisting of halo, oxo, hydroxy,  $C_1$ - $C_3$ -hydrocarbyl, methoxy,  $HalCH_2-O-$ ,  $Hal_2CH-O-$ ,  $Hal_3C-O-$  (preferably  $F_3C-O-$ ),  $NH_2-$ ,  $-N(C_1-C_3alkyl)_2$ , -CN,  $-S(O)_{0-2}-C_1-C_4alkyl$ ,  $-CF_3$ , and mono-, di-, or tri- halo substituted alkyl, or, when there are two optional substituents bonded to adjacent atoms of the phenyl, thienyl, or pyridyl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heteroalkyl having 1, 2, or 3 annular heteroatoms.

[0291] In a preferred embodiment of the compounds according to Formula (III), X is selected from the group consisting of phenyl, pyridyl, thienyl and furyl, each of which is optionally substituted with one, two or three independently selected substituents.

[0292] In a preferred embodiment of the compounds according to Formula (III), X is selected from the group consisting of phenyl, pyridyl, thienyl and furyl, each of which is optionally substituted with one, two or three substituents independently selected from the group consisting of halo, oxo, hydroxy,  $C_1$ - $C_3$ -hydrocarbyl, methoxy,  $HalCH_2-O-$ ,  $Hal_2CH-O-$ ,  $Hal_3C-O-$  (preferably  $F_3C-O-$ ),  $NH_2-$ ,  $-N(C_1-C_3alkyl)_2$ , -CN,  $-S(O)_{0-2}-C_1-C_4alkyl$ ,  $-CF_3$ , and mono-, di-, or tri- halo substituted alkyl, or, when there are two optional substituents bonded to adjacent atoms of the phenyl, thienyl, or pyridyl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heteroalkyl having 1, 2, or 3 annular heteroatoms.

[0293] In a preferred embodiment of the compounds according to Formula (III), Ar is optionally substituted with one or two substituents independently selected from the group consisting of halo, nitro, hydroxy,  $C_1$ - $C_3$ -hydrocarbyl, methoxy,  $HalCH_2-O-$ ,  $Hal_2CH-O-$ ,  $Hal_3C-O-$  (preferably  $F_3C-O-$ ), and mono-, di-, or tri- halo substituted alkyl.

[0294] In a preferred embodiment of the compounds according to Formula (III), Ar is selected from the group consisting of phenyl, pyridyl, pyrimidyl, benzofuryl, benzothienyl, thienyl and furanyl, each of which is optionally substituted with one or two substituents.

[0295] In a preferred embodiment of the compounds according to Formula (III), Ar is selected from the group consisting of phenyl, pyridyl, pyrimidyl, benzofuryl, benzothienyl,



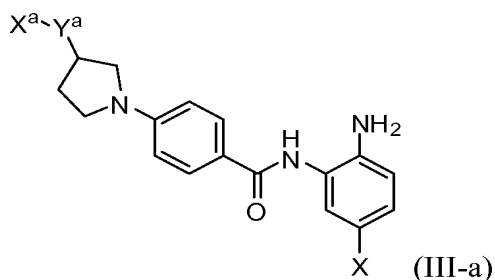
thienyl and furanyl, each of which is optionally substituted with one or two substituents independently selected from the group consisting of halo, nitro, hydroxy, C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl, methoxy, HalCH<sub>2</sub>-O-, Hal<sub>2</sub>CH-O-, Hal<sub>3</sub>C-O- (preferably F<sub>3</sub>C-O-), and mono-, di-, or tri- halo substituted alkyl.

**[0296]** In a preferred embodiment of the compounds according to Formula (III), X<sup>a</sup> comprises a moiety selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycyl, each of which is optionally substituted with from 1 to 3 independently selected substituents.

**[0297]** In a preferred embodiment of the compounds according to Formula (III), X<sup>a</sup> comprises a moiety selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycyl, each of which is optionally substituted with from 1 to 3 substituents independently selected from the group consisting of -OH, -NH<sub>2</sub>, -O-C<sub>0</sub>-C<sub>3</sub>alkylCH<sub>3</sub>, halo, oxo, -C(O)NH<sub>2</sub>, -NHC(O)CH<sub>3</sub>.

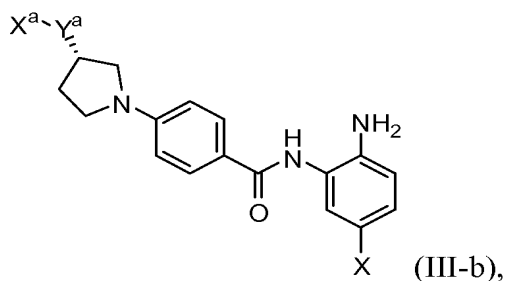
**[0298]** In a preferred embodiment of the compounds according to Formula (III), X<sup>a</sup>-Y<sup>a</sup>- is selected from the group consisting of CH<sub>3</sub>-SO<sub>2</sub>-, CF<sub>3</sub>-C(O)-NH-, CH<sub>3</sub>-C(O)-NH-, ((CH<sub>3</sub>)<sub>2</sub>N)<sub>2</sub>-C=N-, (CH<sub>3</sub>)<sub>2</sub>N-, CH<sub>3</sub>-O-CH<sub>2</sub>-C(O)-NH-, (CH<sub>3</sub>)<sub>2</sub>N-CH<sub>2</sub>-C(O)-NH-, CH<sub>3</sub>CH<sub>2</sub>-N(CH<sub>3</sub>)-, CF<sub>3</sub>CH<sub>2</sub>-NH-, H-, HO-, CH<sub>3</sub>-O-C(O)-NH-, H<sub>2</sub>N-, CH<sub>3</sub>CH<sub>2</sub>-NH-, H<sub>2</sub>N-C(O)-, phenyl-CH<sub>2</sub>-O-C(O)-N(CH<sub>2</sub>CH<sub>3</sub>)-, CH<sub>3</sub>CH<sub>2</sub>-NH-, F, CH<sub>3</sub>-O-CH<sub>2</sub>-C(O)-NH-, heterocyclyl-heterocyclyl, heterocyclyl-heteroaryl, aryl-NH-, heteroaryl-NH-, (CH<sub>3</sub>)<sub>2</sub>N-CH<sub>2</sub>-C(O)-NH- and HO-CH<sub>2</sub>CH<sub>2</sub>-NH-.

**[0299]** In a preferred embodiment of the compounds according to Formula (III), the compounds are represented by the formula (III-a):



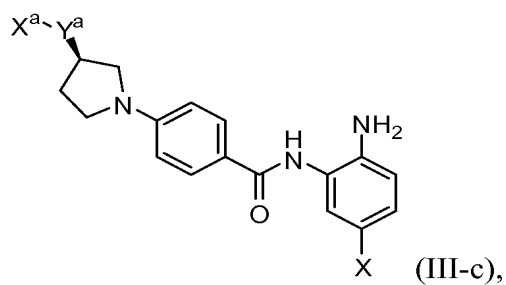
wherein X, X<sup>a</sup> and Y<sup>a</sup> are as defined for Formula (III).

**[0300]** In a preferred embodiment of the compounds according to Formula (III), the compounds are represented by the formula (III-b):



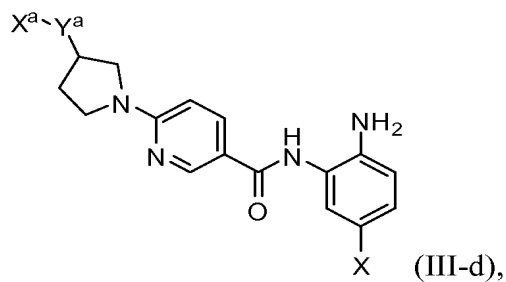
wherein X, X<sup>a</sup> and Y<sup>a</sup> are as defined for Formula (III).

**[0301]** In a preferred embodiment of the compounds according to Formula (III), the compounds are represented by the formula (III-c):



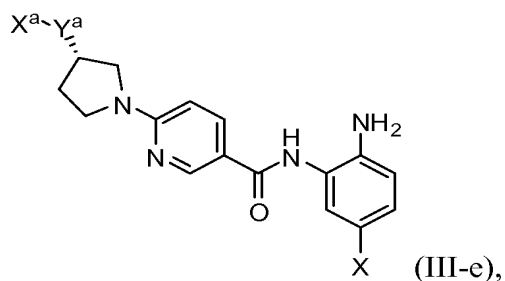
wherein X, X<sup>a</sup> and Y<sup>a</sup> are as defined for Formula (III).

**[0302]** In a preferred embodiment of the compounds according to Formula (III), the compounds are represented by the formula (III-d):



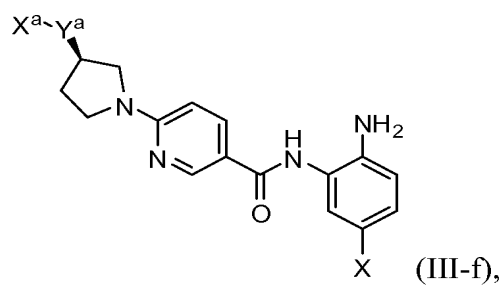
wherein X, X<sup>a</sup> and Y<sup>a</sup> are as defined for Formula (III).

**[0303]** In a preferred embodiment of the compounds according to Formula (III), the compounds are represented by the formula (III-e):



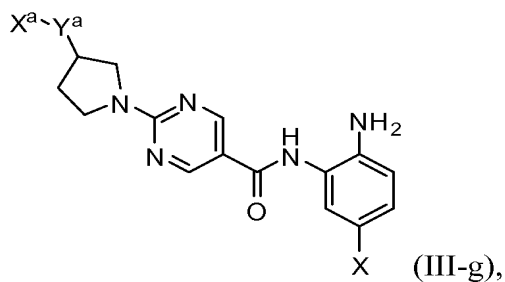
wherein X, X<sup>a</sup> and Y<sup>a</sup> are as defined for Formula (III).

**[0304]** In a preferred embodiment of the compounds according to Formula (III), the compounds are represented by the formula (III-f):



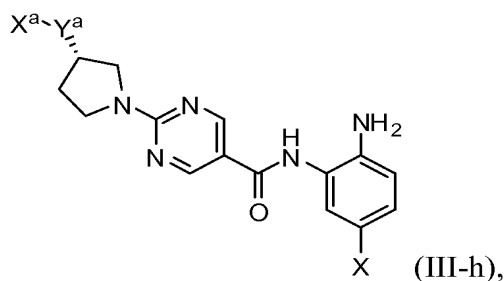
wherein X, X<sup>a</sup> and Y<sup>a</sup> are as defined for Formula (III).

**[0305]** In a preferred embodiment of the compounds according to Formula (III), the compounds are represented by the formula (III-g):



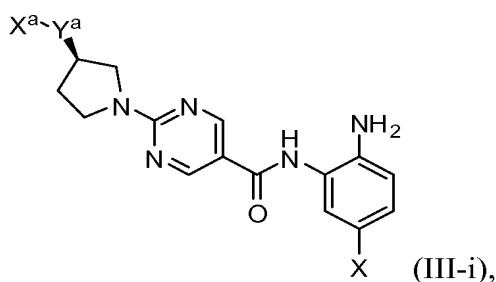
wherein X, X<sup>a</sup> and Y<sup>a</sup> are as defined for Formula (III).

**[0306]** In a preferred embodiment of the compounds according to Formula (III), the compounds are represented by the formula (III-h):



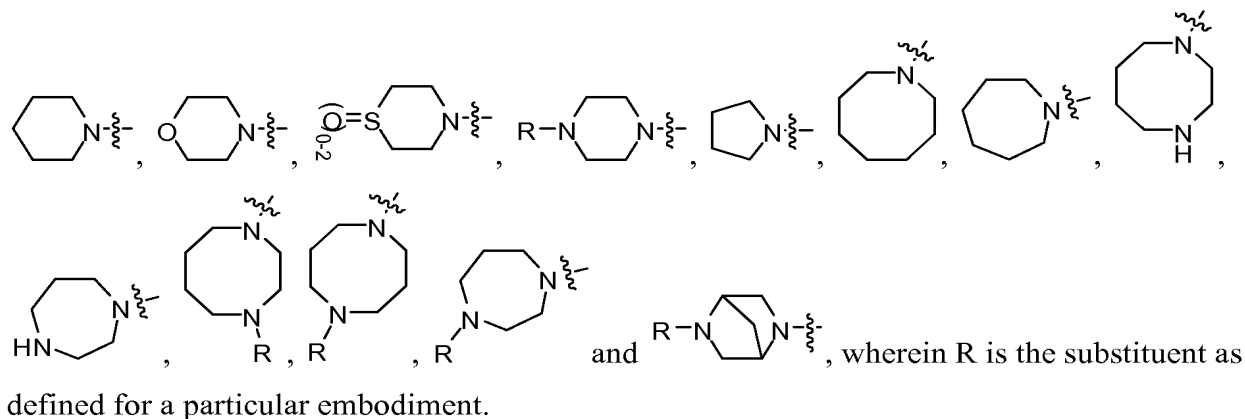
wherein X, X<sup>a</sup> and Y<sup>a</sup> are as defined for Formula (III).

[0307] In a preferred embodiment of the compounds according to Formula (III), the compounds are represented by the formula (III-i):



wherein X, X<sup>a</sup> and Y<sup>a</sup> are as defined for Formula (III).

[0308] In a preferred embodiment of the compounds according to the present invention, when a moiety is defined as -N(R<sup>x</sup>)(R<sup>y</sup>), wherein R<sup>x</sup> and R<sup>y</sup>, together with the N atom to which they are attached optionally form a heterocycle with one or more annular heteroatoms, said heterocycle is selected from the group consisting of



[0309] In another embodiment, the invention comprises the following compounds:

Cpd	Name
30	N-(2-amino-5-(benzo[d][1,3]dioxol-5-yl)phenyl)-4-(morpholinomethyl)benzamide

Cpd	Name
33	(E)-N-(2-amino-5-(3-methoxyprop-1-enyl)phenyl)-4-(morpholinomethyl)benzamide
66	N-(2-amino-5-(thiophen-2-yl)phenyl)-1,3-dimethyl-1H-thieno[2,3-c]pyrazole-5-carboxamide
72	2-(4-(((6-chloro-5-fluoro-1H-benzo[d]imidazol-2-ylthio)methyl)benzamido)-4-(thiophen-2-yl)benzoic acid
132	N-(2-Amino-5-(thiophen-2-yl)phenyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamide
161	(S)-2-(5-(2-Amino-5-(thiophen-2-yl)phenylcarbonyl)-2-methyl-1H-benzo[d]imidazol-1-yl)ethyl 2-(tert-butoxycarbonylamino)-3-methylbutanoate
172	2-(4-(((6-chloro-5-fluoro-1H-benzo[d]imidazol-2-ylthio)methyl)benzamido)-4-(thiophen-2-yl)benzoic acid
184	N-1-(2-Amino-5-(thiophen-2-yl)phenyl)-N8-(biphenyl-3-yl)octanediamide
193	N-(2-Amino-5-(5-((2-hydroxyethylamino)methyl)thiophen-2-yl)phenyl)-4-methoxybenzamide
194	N-(5-(5-((1H-pyrazol-5-ylamino)methyl)thiophen-2-yl)-2-aminophenyl)-4-methoxybenzamide
201	N-(2-Amino-5-(5-((hydroxyimino)methyl)thiophen-2-yl)phenyl)-4-(pyridin-3-yl)benzamide
205	N-(2-Amino-5-(thiophen-2-yl)phenyl)-2-(1-benzylpiperidin-4-ylidene)acetamide
210	N-(4-Amino-4'-(methylsulfinyl)biphenyl-3-yl)-4-methoxybenzamide
216	Pyridin-3-ylmethyl 6-(2-amino-5-(thiophen-2-yl)phenylcarbonyl)-3,4-dihydroquino-line-1(2H)-carboxylate
222	N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(((3-(2-(dimethylamino)ethyl)-3-methylureido)methyl)benzamide
279	N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-yl)butanamide
316	N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazine-1-carboxamide
320	N-(4-Aminobiphenyl-3-yl)-1-(4-nitrophenylsulfonyl)piperidine-4-carboxamide

[0310] In preferred embodiments of the present invention, the invention comprises the following compounds:

[0311] N-(2-amino-5-(1H-indol-5-yl)phenyl)-4-methoxybenzamide,

[0312] (tetrahydro-2H-pyran-2-yl)methyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbonyl)phenylcarbamate,

[0313] N-(2-amino-5-(thiophen-2-yl)phenyl)-3-(pyridin-3-yl)benzamide,

[0314] N-(2-amino-5-(1H-pyrrol-2-yl)phenyl)-4-methoxybenzamide,

- [0315] N-(2-amino-5-(1H-pyrrol-2-yl)phenyl)-4-(pyridin-3-yl)benzamide,
- [0316] N-(2-amino-5-(pyridin-3-yl)phenyl)-4-(pyridin-3-yl)benzamide,
- [0317] pyridin-3-ylmethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0318] N-(2-amino-5-(thiophen-2-yl)phenyl)-5-(pyridin-2-yl)thiophene-2-carboxamide,
- [0319] N-(4,4'-diaminobiphenyl-3-yl)-4-(pyridin-3-yl)benzamide,
- [0320] (S)-2-(5-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)ethyl 2-amino-3-methylbutanoate,
- [0321] N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(pyridin-3-yl)benzamide,
- [0322] N-(2-amino-5-(thiophen-2-yl)phenyl)-3',4',5'-trimethoxybiphenyl-3-carboxamide,
- [0323] N-(2-amino-5-(thiophen-2-yl)phenyl)-3-(1H-pyrazol-4-yl)benzamide,
- [0324] N-(2-amino-5-(1H-pyrazol-4-yl)phenyl)-4-(pyridin-3-yl)benzamide,
- [0325] N-(2-amino-5-(thiophen-2-yl)phenyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamide,
- [0326] 2-(4-((6-chloro-5-fluoro-1H-benzo[d]imidazol-2-ylthio)methyl)benzamido)-4-(thiophen-2-yl)benzoic acid,
- [0327] 4-acetamido-N-(2-amino-5-(thiophen-2-yl)phenyl)-3-hydroxybenzamide,
- [0328] N1-(2-amino-5-(thiophen-2-yl)phenyl)-N8-(biphenyl-3-yl)octanediamide,
- [0329] N-(4-aminobiphenyl-3-yl)-4-(morpholinomethyl)benzamide,
- [0330] N-(4-aminobiphenyl-3-yl)-4-(pyridin-3-yl)benzamide,
- [0331] N-(2-amino-5-(5-((2-hydroxyethylamino)methyl)thiophen-2-yl)phenyl)-4-methoxybenzamide,
- [0332] N-(5-(5-((1H-pyrazol-5-ylamino)methyl)thiophen-2-yl)-2-aminophenyl)-4-methoxybenzamide,
- [0333] N-(2-amino-5-(5-chlorothiophen-2-yl)phenyl)-4-(pyridin-3-yl)benzamide,
- [0334] (E)-N-(2-amino-5-(thiophen-2-yl)phenyl)-3-(6-(3,4,5-trimethoxyphenyl)pyridin-3-yl)acrylamide,
- [0335] (E)-3-(2,3'-bipyridin-5-yl)-N-(2-amino-5-(thiophen-2-yl)phenyl)acrylamide,
- [0336] (E)-N-(2-amino-5-(thiophen-2-yl)phenyl)-3-(6-(3,4-dimethoxyphenyl)pyridin-3-yl)acrylamide,
- [0337] N-(2-amino-5-(thiophen-2-yl)phenyl)-6-chloronicotinamide,
- [0338] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(piperidin-1-ylmethyl)benzamide,

- [0339] N-(2-amino-5-(thiophen-2-yl)phenyl)-6-morpholinonicotinamide,
- [0340] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-hydroxypyrrolidin-1-yl)methyl)benzamide,
- [0341] (R)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide,
- [0342] (S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)benzamide,
- [0343] N-(2-amino-5-(thiophen-2-yl)phenyl)-6-(4-methylpiperazin-1-yl)nicotinamide,
- [0344] (Z)-N-(2-amino-5-(5-((hydroxyimino)methyl)thiophen-2-yl)phenyl)-4-(pyridin-3-yl)benzamide,
- [0345] N-(2-amino-5-(thiophen-2-yl)phenyl)-2-ethoxypyrimidine-5-carboxamide,
- [0346] N-(4-amino-4'-(methylthio)biphenyl-3-yl)-4-methoxybenzamide,
- [0347] N-(4-amino-4'-(methylsulfinyl)biphenyl-3-yl)-4-methoxybenzamide,
- [0348] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((ethyl(methyl)amino)methyl)benzamide,
- [0349] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-isopropylpiperazin-1-yl)methyl)benzamide,
- [0350] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-(2-methoxyethyl)piperazin-1-yl)methyl)benzamide,
- [0351] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-cyclopentylpiperazin-1-yl)methyl)benzamide,
- [0352] N-(2-amino-5-(thiophen-2-yl)phenyl)-2-morpholinopyrimidine-5-carboxamide,
- [0353] N-(2-amino-5-(thiophen-2-yl)phenyl)-2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxamide,
- [0354] (R)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-hydroxypiperidin-1-yl)methyl)benzamide,
- [0355] N-(2-amino-5-(pyridin-3-yl)phenyl)-4-(morpholinomethyl)benzamide,
- [0356] N-(2-amino-5-(thiophen-2-yl)phenyl)-1,3-dimethyl-1H-thieno[2,3-c]pyrazole-5-carboxamide,
- [0357] N-(2-amino-5-(pyridin-4-yl)phenyl)-4-(morpholinomethyl)benzamide,
- [0358] (R)-N-(2-amino-5-(pyridin-3-yl)phenyl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide,

- [0359] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-(2-methoxyethyl)piperazin-1-yl)benzamide,
- [0360] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(2-(dimethylamino)ethylthio)benzamide,
- [0361] N-(4-amino-4'-hydroxybiphenyl-3-yl)-4-(morpholinomethyl)benzamide,
- [0362] (R)-N-(4-aminobiphenyl-3-yl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide,
- [0363] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-cyclopentylpiperazin-1-yl)benzamide,
- [0364] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-(pyrrolidin-1-yl)piperidin-1-yl)benzamide,
- [0365] (R)-N-(4-amino-4'-hydroxybiphenyl-3-yl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide,
- [0366] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((bis(2-methoxyethyl)amino)methyl)benzamide,
- [0367] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-isopropylpiperazin-1-yl)benzamide,
- [0368] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-morpholinopiperidin-1-yl)benzamide,
- [0369] (R)-N-(2-amino-5-(thiophen-2-yl)phenyl)-6-(3-(dimethylamino)pyrrolidin-1-yl)nicotinamide,
- [0370] N-(2-amino-5-(thiophen-2-yl)phenyl)-6-(2-(pyrrolidin-1-yl)ethyl)nicotinamide,
- [0371] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(2-(diethylamino)ethylthio)benzamide,
- [0372] (S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((2-(methoxymethyl)pyrrolidin-1-yl)methyl)benzamide,
- [0373] 2-(dimethylamino)ethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)benzylcarbamate,
- [0374] N-(2-amino-5-(thiophen-2-yl)phenyl)-2-(4-morpholinopiperidin-1-yl)pyrimidine-5-carboxamide,
- [0375] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-morpholinopiperidin-1-yl)methyl)benzamide,
- [0376] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)benzamide,
- [0377] (E)-N-(2-amino-5-(thiophen-2-yl)phenyl)-3-(6-morpholinopyridin-3-yl)acrylamide,
- [0378] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide,
- [0379] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((diethylamino)methyl)benzamide,



- [0380] 4-((4-(2-(1H-imidazol-1-yl)ethyl)piperazin-1-yl)methyl)-N-(2-amino-5-(thiophen-2-yl)phenyl)benzamide,
- [0381] N-(2-amino-5-(thiophen-2-yl)phenyl)quinoline-3-carboxamide,
- [0382] 3-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl acetate,
- [0383] N-(2-amino-5-(thiophen-2-yl)phenyl)-3-hydroxybenzamide,
- [0384] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(isoindolin-2-ylmethyl)benzamide,
- [0385] (S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide,
- [0386] (S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-hydroxypyrrolidin-1-yl)methyl)benzamide,
- [0387] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-(2-(dimethylamino)ethyl)-3-methylureido)methyl)benzamide,
- [0388] N-(2-amino-5-(thiophen-3-yl)phenyl)-4-(morpholinomethyl)benzamide,
- [0389] (R)-4-((3-acetamidopyrrolidin-1-yl)methyl)-N-(2-amino-5-(thiophen-2-yl)phenyl)benzamide
- [0390] (R)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-hydroxypyrrolidin-1-yl)methyl)benzamide
- [0391] (R)-N-(2-amino-5-(thiophen-3-yl)phenyl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide,
- [0392] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-(pyridin-4-yl)piperazin-1-yl)methyl)benzamide,
- [0393] (S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)methyl)benzamide,
- [0394] N-(2-amino-5-(thiophen-2-yl)phenyl)-5-(morpholinomethyl)furan-2-carboxamide,
- [0395] (S)-4-((3-acetamidopyrrolidin-1-yl)methyl)-N-(2-amino-5-(thiophen-2-yl)phenyl)benzamide,
- [0396] (S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(3-(pyridin-3-ylamino)pyrrolidin-1-yl)benzamide,
- [0397] 3-(3-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl)propanoic acid,
- [0398] 3-(4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl)propanoic acid,
- [0399] N-(2-amino-5-(furan-3-yl)phenyl)-4-(morpholinomethyl)benzamide,

- [0400] N-(4-amino-4'-chlorobiphenyl-3-yl)-4-(morpholinomethyl)benzamide,
- [0401] (S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-(dimethylamino)-2,5-dioxopyrrolidin-1-yl)methyl)benzamide,
- [0402] N-(2-amino-5-(6-fluoropyridin-3-yl)phenyl)-4-(morpholinomethyl)benzamide,
- [0403] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((methyl(pyridin-3-yl)methyl)amino)methyl)benzamide,
- [0404] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-(pyridin-2-yl)piperazin-1-yl)methyl)benzamide,
- [0405] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(pyrrolidin-1-ylmethyl)benzamide,
- [0406] N-(2-amino-5-(5-cyanothiophen-2-yl)phenyl)-4-(morpholinomethyl)benzamide,
- [0407] (S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-(pyridin-3-ylamino)pyrrolidin-1-yl)methyl)benzamide,
- [0408] methyl 3-(4-(2-amino-5-(thiophen-2-yl)phenylcarbonyl)phenyl)propanoate,
- [0409] N-(2-amino-5-(thiophen-2-yl)phenyl)-6-(1H-pyrazol-1-yl)nicotinamide,
- [0410] N-(2-amino-5-(benzo[d][1,3]dioxol-5-yl)phenyl)-4-(morpholinomethyl)benzamide,
- [0411] N-(2-amino-5-(5-methylthiophen-2-yl)phenyl)-4-(morpholinomethyl)benzamide,
- [0412] pyridin-3-ylmethyl 6-(2-amino-5-(thiophen-2-yl)phenylcarbonyl)-3,4-dihydroquinoline-1(2H)-carboxylate,
- [0413] N-(4-amino-3'-(trifluoromethoxy)biphenyl-3-yl)-4-(morpholinomethyl)benzamide,
- [0414] N-(2-amino-5-(thiophen-2-yl)phenyl)-6-bromonicotinamide,
- [0415] N-(2-amino-5-(thiophen-2-yl)phenyl)-6-(4-morpholinopiperidin-1-yl)nicotinamide,
- [0416] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-benzylpiperazin-1-yl)methyl)benzamide,
- [0417] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(((2R,5R)-2,5-dimethylpyrrolidin-1-yl)methyl)benzamide,
- [0418] (E)-3-(4-(2-amino-5-(thiophen-2-yl)phenylcarbonyl)phenyl)acrylic acid,
- [0419] (E)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(3-(hydroxyamino)-3-oxoprop-1-enyl)benzamide,
- [0420] N-(2-amino-5-(5-chlorothiophen-2-yl)phenyl)-4-(morpholinomethyl)benzamide,
- [0421] N-(2-amino-5-(3-hydroxycyclopent-1-enyl)phenyl)-4-(morpholinomethyl)benzamide,
- [0422] 4-(2-amino-5-(thiophen-2-yl)phenylcarbonyl)benzoic acid,
- [0423] N-(2-amino-5-(5-chlorothiophen-2-yl)phenyl)-4-(4-methylpiperazin-1-yl)benzamide,

- [0424] N-(2-amino-5-(5-chlorothiophen-2-yl)phenyl)-4-(3-morpholinopyrrolidin-1-yl)benzamide,
- [0425] methyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)benzoate,
- [0426] N1-(2-amino-5-(thiophen-2-yl)phenyl)-N4-hydroxyterephthalamide,
- [0427] 4-(2-amino-5-(3-hydroxycyclopent-1-enyl)phenylcarbamoyl)phenyl acetate,
- [0428] N-(2-amino-5-(3-hydroxycyclopent-1-enyl)phenyl)-4-hydroxybenzamide,
- [0429] N-(2-amino-5-(thiophen-2-yl)phenyl)-5-bromo-6-oxo-1,6-dihydropyridine-3-carboxamide,
- [0430] N-(2-amino-5-(thiophen-2-yl)phenyl)-6-cyanonicotinamide,
- [0431] 2-(dimethylamino)ethyl 4-(2-amino-5-(thiophen-3-yl)phenylcarbamoyl)phenylcarbamate,
- [0432] 2-(dimethylamino)ethyl 4-(4-amino-4'-chloro-3'-fluorobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0433] 2-(dimethylamino)ethyl 4-(4-amino-3'-fluorobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0434] 4-(2-amino-5-(thiophen-3-yl)phenylcarbamoyl)phenyl acetate,
- [0435] N-(2-amino-5-(thiophen-3-yl)phenyl)-4-hydroxybenzamide,
- [0436] N-(2-amino-5-(thiophen-3-yl)phenyl)acetamide,
- [0437] N-(2-amino-5-(thiophen-2-yl)phenyl)-6-carbamimidoylnicotinamide,
- [0438] N-(2-amino-5-(thiophen-2-yl)phenyl)-6-(thiophen-2-yl)nicotinamide,
- [0439] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-(pyridin-4-yl)piperazin-1-yl)benzamide,
- [0440] 2-(dimethylamino)ethyl 4-(2-amino-5-(6-chloropyridin-3-yl)phenylcarbamoyl)phenylcarbamate,
- [0441] N-(2-amino-5-(6-chloropyridin-3-yl)phenyl)-4-hydroxybenzamide,
- [0442] 2-(dimethylamino)ethyl 4-(2-amino-5-(pyridin-3-yl)phenylcarbamoyl)phenylcarbamate,
- [0443] N-(2-amino-5-(thiophen-2-yl)phenyl)-3-fluoro-4-hydroxybenzamide,
- [0444] N-(2-amino-5-(6-fluoropyridin-3-yl)phenyl)-4-hydroxybenzamide,
- [0445] 2-(dimethylamino)ethyl 4-(2-amino-5-(6-fluoropyridin-3-yl)phenylcarbamoyl)phenylcarbamate,
- [0446] N-(2-amino-5-(pyridin-3-yl)phenyl)-4-hydroxybenzamide,

- [0447] 4-(2-amino-5-(6-fluoropyridin-3-yl)phenylcarbamoyl)phenyl acetate,
- [0448] N-(2-amino-5-(5-chlorothiophen-2-yl)phenyl)-4-(4-(pyridin-4-yl)piperazin-1-yl)benzamide,
- [0449] pyridin-3-ylmethyl 3-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0450] 2-(dimethylamino)ethyl 4-(4-amino-3',4'-dichlorobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0451] 2-morpholinoethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0452] 2-(pyrrolidin-1-yl)ethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0453] (S)-(1-methylpyrrolidin-2-yl)methyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0454] (2E,4Z)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-ylidene)but-2-enamide,
- [0455] (E)-N-(2-amino-5-(thiophen-2-yl)phenyl)-3-(4-(morpholinomethyl)phenyl)acrylamide,
- [0456] 4-(4-amino-3',4'-dichlorobiphenyl-3-ylcarbamoyl)phenyl acetate,
- [0457] 2-(dimethylamino)ethyl 4-(4-amino-3',4'-difluorobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0458] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-yl)butanamide,
- [0459] 4-(4-amino-3',4'-difluorobiphenyl-3-ylcarbamoyl)phenyl acetate,
- [0460] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-(pyridin-3-yl)thiazol-2-ylamino)benzamide,
- [0461] N-(4-amino-3',4'-difluorobiphenyl-3-yl)-4-hydroxybenzamide,
- [0462] 2-(dimethylamino)ethyl 4-(4-aminobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0463] N-(2-amino-5-(thiophen-2-yl)phenyl)-5-(3-(dimethylamino)prop-1-ynyl)nicotinamide,
- [0464] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(pyrrolidin-1-yl)benzamide,
- [0465] (E)-N-(2-amino-5-(thiophen-2-yl)phenyl)-3-(4-(hydroxymethyl)phenyl)acrylamide,
- [0466] (S)-N-(4-aminobiphenyl-3-yl)-4-(3-aminopyrrolidin-1-yl)benzamide,
- [0467] N-(4-aminobiphenyl-3-yl)-4-hydroxybenzamide,

- [0468] 2-(methyl(pyridin-2-yl)amino)ethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0469] N-(2-amino-5-(thiophen-2-yl)phenyl)-5-((4-morpholinopiperidin-1-yl)methyl)furan-2-carboxamide,
- [0470] 2-(4-methylpiperazin-1-yl)ethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0471] 2-(dimethylamino)ethyl 4-(2-hydroxy-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0472] 4-hydroxy-N-(2-hydroxy-5-(thiophen-2-yl)phenyl)benzamide,
- [0473] N-(4-aminobiphenyl-3-yl)-1-(4-nitrophenylsulfonyl)piperidine-4-carboxamide,
- [0474] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(piperazin-1-ylmethyl)benzamide,
- [0475] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazine-1-carboxamide,
- [0476] (S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(3-aminopyrrolidin-1-yl)benzamide,
- [0477] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(piperidin-1-yl)benzamide,
- [0478] N-(2-hydroxy-5-(thiophen-3-yl)phenyl)-4-(morpholinomethyl)benzamide,
- [0479] 3-(dimethylamino)propyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0480] 2-morpholinoethyl 4-(4-aminobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0481] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(piperazin-1-yl)benzamide,
- [0482] 2-(dimethylamino)ethyl 4-(2-hydroxy-5-(thiophen-3-yl)phenylcarbamoyl)phenylcarbamate,
- [0483] 2-(dimethylamino)ethyl 4-(2-amino-5-(5-chlorothiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0484] 2-(pyrrolidin-1-yl)ethyl 3-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0485] (E)-3-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)-N-(2-amino-5-(thiophen-2-yl)phenyl)acrylamide,
- [0486] 1-methylpiperidin-4-yl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,

- [0487] (R)-1-methylpyrrolidin-3-yl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0488] 2-(dimethylamino)ethyl 4-(2-amino-5-(6-methoxypyridin-3-yl)phenylcarbamoyl)phenylcarbamate,
- [0489] 2-(dimethylamino)ethyl 4-(2-amino-5-(pyridin-4-yl)phenylcarbamoyl)phenylcarbamate,
- [0490] 2-(dimethylamino)ethyl 4-(2-amino-5-(2-methoxypyridin-3-yl)phenylcarbamoyl)phenylcarbamate,
- [0491] 2-(dimethylamino)ethyl 4-(4-amino-3'-(trifluoromethoxy)biphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0492] N-(4-(4-aminobiphenyl-3-ylcarbamoyl)benzyl)-2-(methylsulfonamido)benzamide,
- [0493] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-(pyridin-3-ylmethyl)piperazin-1-yl)benzamide,
- [0494] 2-(dimethylamino)ethyl 4-(4-amino-4'-(trifluoromethoxy)biphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0495] 2-(dimethylamino)ethyl 4-(4-amino-3'-fluoro-4'-methoxybiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0496] 2-(dimethylamino)ethyl 4-(4-amino-4'-fluorobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0497] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-(pyridin-4-ylmethyl)piperazin-1-yl)benzamide,
- [0498] 2-(dimethylamino)ethyl 4-(4-amino-4'-chlorobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0499] 2-(dimethylamino)ethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)piperidine-1-carboxylate,
- [0500] N-(2-amino-5-(pyridin-3-yl)phenyl)-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide,
- [0501] 2-(dimethylamino)ethyl (1r,4r)-4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)cyclohexylcarbamate,
- [0502] 2-(dimethylamino)ethyl 4-(4-amino-3'-fluoro-4'-hydroxybiphenyl-3-ylcarbamoyl)phenylcarbamate,

- [0503] N-(2-amino-5-(thiophen-2-yl)phenyl)-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide,
- [0504] 2-(dimethylamino)ethyl 4-(4-amino-2',4'-difluorobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0505] 2-(dimethylamino)ethyl 4-(4-amino-4'-(trifluoromethyl)biphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0506] 2-(dimethylamino)ethyl 4-(4-amino-2'-fluorobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0507] 2-(dimethylamino)ethyl 4-(4-amino-4'-hydroxybiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0508] 2-(dimethylamino)ethyl 4-(4-amino-3',4',5'-trifluorobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0509] 2-(dimethylamino)ethyl 4-(4-amino-4'-(dimethylamino)biphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0510] 2-(dimethylamino)ethyl 4-(4-amino-4'-(methylthio)biphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0511] 2-(dimethylamino)ethyl 4-(4-amino-4'-cyanobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0512] 2-(dimethylamino)ethyl 5-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)thiophen-2-ylcarbamate,
- [0513] 2-(dimethylamino)ethyl 4-(4-amino-2'-fluoro-4'-methoxybiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0514] 2-(dimethylamino)ethyl 4-(4-amino-3'-fluoro-4'-methylbiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0515] 2-(dimethylamino)ethyl 4-(2-amino-5-(thiazol-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0516] N-(2-amino-5-(thiazol-2-yl)phenyl)-4-(4-methylpiperazin-1-yl)benzamide,
- [0517] 2-(dimethylamino)ethyl 4-(4-amino-2',4',5'-trifluorobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0518] 2-(dimethylamino)ethyl 4-(4-amino-4'-(methylsulfinyl)biphenyl-3-ylcarbamoyl)phenylcarbamate,

- [0519] 2-(dimethylamino)ethyl 4-(4-amino-2'-fluoro-4'-(trifluoromethyl)biphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0520] 2-(dimethylamino)ethyl 4-(4-amino-4'-(methylsulfonyl)biphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0521] 2-(dimethylamino)ethyl 4-(4,4'-diaminobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0522] N-(2-amino-5-(thiophen-2-yl)phenyl)-1-(benzo[d][1,3]dioxol-5-ylmethyl)-1H-1,2,3-triazole-4-carboxamide,
- [0523] 2-(dimethylamino)ethyl 4-(4-amino-4'-ethoxybiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0524] 2-(dimethylamino)ethyl 4-(2-amino-5-(5-(methylthio)thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0525] 4-methoxy-N-(2-(sulfamoylamino)-5-(thiophen-2-yl)phenyl)benzamide,
- [0526] (S)-4-(3-acetamidopyrrolidin-1-yl)-N-(4-aminobiphenyl-3-yl)benzamide,
- [0527] (S)-4-(3-acetamidopyrrolidin-1-yl)-N-(4-amino-4'-fluorobiphenyl-3-yl)benzamide,
- [0528] 2-(dimethylamino)ethyl 4-(4-amino-4'-cyano-3'-fluorobiphenyl-3-ylcarbamoyl)phenylcarbamate,
- [0529] N-(2-amino-5-(thiophen-2-yl)phenyl)-3-(4-(morpholinomethyl)phenyl)propanamide,
- [0530] (S)-N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(3-aminopyrrolidin-1-yl)benzamide,
- [0531] (S)-N-(4-aminobiphenyl-3-yl)-4-(3-(bis(dimethylamino)methyleneamino)pyrrolidin-1-yl)benzamide,
- [0532] 2-(dimethylamino)ethyl 4-(2-amino-5-(2-aminopyrimidin-5-yl)phenylcarbamoyl)phenylcarbamate,
- [0533] (S)-N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(3-(bis(dimethylamino)methyleneamino)pyrrolidin-1-yl)benzamide,
- [0534] N-(2-amino-5-(pyridin-4-yl)phenyl)-3-methoxybenzamide,
- [0535] N-(2-amino-5-(pyridin-4-yl)phenyl)-4-(dimethylamino)benzamide,
- [0536] N-(2-amino-5-(pyridin-4-yl)phenyl)benzofuran-2-carboxamide,
- [0537] N-(4-amino-3',4'-difluorobiphenyl-3-yl)-1-benzylpiperidine-4-carboxamide,
- [0538] 2-(dimethylamino)ethyl 4-(3-fluoro-2-hydroxy-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate,
- [0539] N-(4-amino-3',4'-difluorobiphenyl-3-yl)-4-(1,3-dioxoisindolin-2-yl)benzamide,



- [0540] N-(2-amino-5-(pyridin-4-yl)phenyl)benzo[d][1,3]dioxole-5-carboxamide,
- [0541] N-(2-amino-5-(pyridin-4-yl)phenyl)-4,6-dimethoxybenzofuran-2-carboxamide,
- [0542] N-(2-amino-5-(pyridin-4-yl)phenyl)-6-(2-morpholinoethoxy)benzofuran-2-carboxamide,
- [0543] N-(4-amino-3',4'-difluorobiphenyl-3-yl)-5-(morpholinomethyl)furan-2-carboxamide,
- [0544] N-(2-amino-5-(pyridin-4-yl)phenyl)-4-((3,4-dimethoxyphenylamino)methyl)benzamide,
- [0545] N-(2-amino-5-(pyridin-4-yl)phenyl)-6-(2-(dimethylamino)ethoxy)benzofuran-2-carboxamide,
- [0546] N-(4-aminobiphenyl-3-yl)-6-(2-morpholinoethoxy)benzofuran-2-carboxamide,
- [0547] (S)-benzyl 1-(4-(2-amino-5-(pyridin-4-yl)phenyl)carbonyl)phenylpyrrolidin-3-ylcarbamate,
- [0548] (S)-4-(3-acetamidopyrrolidin-1-yl)-N-(2-amino-5-(pyridin-4-yl)phenyl)benzamide,
- [0549] (S)-N-(2-amino-5-(pyridin-4-yl)phenyl)-4-(3-aminopyrrolidin-1-yl)benzamide,
- [0550] N-(4-aminobiphenyl-3-yl)-5-methyl-4-(morpholinomethyl)furan-2-carboxamide,
- [0551] N-(4-aminobiphenyl-3-yl)-5-(pyridin-2-yl)thiophene-2-carboxamide,
- [0552] N-(4-aminobiphenyl-3-yl)-3-(pyridin-3-yl)benzamide,
- [0553] N-(4-amino-4'-fluorobiphenyl-3-yl)-6-(2-morpholinoethoxy)benzofuran-2-carboxamide,
- [0554] N-(2-amino-5-(pyridin-4-yl)phenyl)-3-fluoro-4-methoxybenzamide,
- [0555] N-(4-aminobiphenyl-3-yl)-1-benzylpiperidine-4-carboxamide,
- [0556] (S)-N-(4-aminobiphenyl-3-yl)-4-(3-(methylsulfonamido)pyrrolidin-1-yl)benzamide,
- [0557] N-(4-aminobiphenyl-3-yl)-4-(4-methylpiperazin-1-yl)benzamide,
- [0558] N-(4-aminobiphenyl-3-yl)-4-(pyrrolidin-1-yl)benzamide,
- [0559] (R)-N-(4-aminobiphenyl-3-yl)-4-(3-aminopyrrolidin-1-yl)benzamide,
- [0560] (S)-N-(4-aminobiphenyl-3-yl)-4-(3-(2,2,2-trifluoroacetamido)pyrrolidin-1-yl)benzamide,
- [0561] N-(4-aminobiphenyl-3-yl)-4-(4-methylpiperazin-1-ylsulfonyl)benzamide,
- [0562] N-(4-amino-3',4'-difluorobiphenyl-3-yl)-6-(2-morpholinoethoxy)benzofuran-2-carboxamide,

- [0563] N-(2-amino-5-(pyridin-4-yl)phenyl)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-2-carboxamide,
- [0564] N-(4-aminobiphenyl-3-yl)-1-benzoylpiperidine-4-carboxamide,
- [0565] (S)-N-(4-aminobiphenyl-3-yl)-4-(3-(dimethylamino)pyrrolidin-1-yl)benzamide,
- [0566] N-(2-amino-5-(thiophen-2-yl)phenyl)-4-benzylpiperazine-1-carboxamide,
- [0567] (R)-N-(4-aminobiphenyl-3-yl)-4-(3-hydroxypyrrolidin-1-yl)benzamide,
- [0568] (S)-methyl 1-(4-(4-aminobiphenyl-3-ylcarbamoyl)phenyl)pyrrolidin-3-ylcarbamate,
- [0569] N-(2-amino-5-(pyridin-4-yl)phenyl)-5,6-dimethoxybenzofuran-2-carboxamide,
- [0570] N-(4-aminobiphenyl-3-yl)-5,6-dimethoxybenzofuran-2-carboxamide,
- [0571] N-(4-aminobiphenyl-3-yl)-4-(4-ethylpiperazin-1-yl)benzamide,
- [0572] N-(4-aminobiphenyl-3-yl)-4-(4-aminopiperidin-1-yl)benzamide,
- [0573] N-(4-aminobiphenyl-3-yl)-4-(3-oxopiperazin-1-yl)benzamide,
- [0574] (S)-N-(4-aminobiphenyl-3-yl)-4-(3-hydroxypyrrolidin-1-yl)benzamide,
- [0575] (S)-benzyl 1-(4-(4-aminobiphenyl-3-ylcarbamoyl)phenyl)pyrrolidin-3-yl(ethyl)carbamate,
- [0576] (S)-N-(4-aminobiphenyl-3-yl)-4-(3-(ethylamino)pyrrolidin-1-yl)benzamide,
- [0577] N-(4-aminobiphenyl-3-yl)-4-(1H-imidazol-1-yl)benzamide,
- [0578] N-(4-amino-4'-fluorobiphenyl-3-yl)-5-(pyridin-2-yl)thiophene-2-carboxamide,
- [0579] (R)-N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(3-aminopyrrolidin-1-yl)benzamide,
- [0580] 1-(4-(4-aminobiphenyl-3-ylcarbamoyl)phenyl)piperidine-4-carboxamide,
- [0581] (S)-N-(4-aminobiphenyl-3-yl)-4-(3-fluoropyrrolidin-1-yl)benzamide,
- [0582] N-(4-aminobiphenyl-3-yl)-4-(3,3-difluoropyrrolidin-1-yl)benzamide,
- [0583] N-(4-amino-4'-fluorobiphenyl-3-yl)-5-phenylfuran-2-carboxamide,
- [0584] (R)-N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(3-(2-methoxyacetamido)pyrrolidin-1-yl)benzamide,
- [0585] (R)-N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(3-(methylsulfonamido)pyrrolidin-1-yl)benzamide,
- [0586] (S)-N-(4-aminobiphenyl-3-yl)-4-(3-(2-methoxyacetamido)pyrrolidin-1-yl)benzamide,
- [0587] (S)-N-(4-aminobiphenyl-3-yl)-4-(3-(2-(dimethylamino)acetamido)pyrrolidin-1-yl)benzamide,
- [0588] (R)-4-(3-acetamidopyrrolidin-1-yl)-N-(4-amino-4'-fluorobiphenyl-3-yl)benzamide,

- [0589] (R)-methyl 1-(4-(4-amino-4'-fluorobiphenyl-3-ylcarbamoyl)phenyl)pyrrolidin-3-ylcarbamate,
- [0590] N-(4-aminobiphenyl-3-yl)-4-(piperazin-1-yl)benzamide,
- [0591] N-(2-amino-5-(pyridin-4-yl)phenyl)quinoxaline-6-carboxamide,
- [0592] N-(4-aminobiphenyl-3-yl)quinoxaline-6-carboxamide,
- [0593] pyridin-3-ylmethyl 4-(2-amino-5-(pyridin-4-yl)phenylcarbamoyl)benzylcarbamate,
- [0594] N-(4-amino-4'-fluorobiphenyl-3-yl)-1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxamide,
- [0595] N-(2-amino-5-(pyridin-4-yl)phenyl)-4-((4-(pyridin-3-yl)pyrimidin-2-ylamino)methyl)benzamide,
- [0596] (Z)-N-(2-amino-5-(pyridin-4-yl)phenyl)-4-(dibenzo[b,f][1,4]oxazepin-11-yl)benzamide,
- [0597] (E)-N-(2-amino-5-(pyridin-4-yl)phenyl)-11-(4-methylpiperazin-1-yl)dibenzo[b,f][1,4]oxazepine-8-carboxamide,
- [0598] (E)-N-(4-aminobiphenyl-3-yl)-11-(4-methylpiperazin-1-yl)dibenzo[b,f][1,4]oxazepine-8-carboxamide,
- [0599] (S)-N-(4-aminobiphenyl-3-yl)-4-(3-(2-hydroxyethylamino)pyrrolidin-1-yl)benzamide,
- [0600] N-(4-aminobiphenyl-3-yl)-5-methoxypicolinamide,
- [0601] N-(4-aminobiphenyl-3-yl)-5-(morpholinomethyl)thiophene-2-carboxamide,
- [0602] (S)-N-(4-aminobiphenyl-3-yl)-4-(3-(2,2,2-trifluoroethylamino)pyrrolidin-1-yl)benzamide,
- [0603] (R)-N-(4-aminobiphenyl-3-yl)-4-(3-(dimethylamino)pyrrolidin-1-yl)benzamide,
- [0604] (R)-N-(4-aminobiphenyl-3-yl)-4-(3-(ethylamino)pyrrolidin-1-yl)benzamide,
- [0605] N-(4-aminobiphenyl-3-yl)-4-(hydroxymethyl)benzamide,
- [0606] (R)-N-(4-aminobiphenyl-3-yl)-4-(3-methoxypyrrolidin-1-yl)benzamide,
- [0607] N-(4-amino-4'-fluorobiphenyl-3-yl)-5,6-dimethoxybenzofuran-2-carboxamide,
- [0608] (S)-methyl 8-(1-(4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl)pyrrolidin-3-ylamino)-8-oxooctanoate,
- [0609] N-(4-aminobiphenyl-3-yl)-6-(piperidin-4-yloxy)benzofuran-2-carboxamide,
- [0610] 4-(4-amino-3-(4-methoxybenzamido)phenyl)pyridine 1-oxide,

- [0611] N-(4-aminobiphenyl-3-yl)-2,3,4,9-tetrahydro-1H-carbazole-6-carboxamide,  
[0612] N-(4-aminobiphenyl-3-yl)-5,6-dimethoxybenzo[b]thiophene-2-carboxamide,  
[0613] N-(4-amino-4'-fluorobiphenyl-3-yl)-6-(piperidin-4-yloxy)benzofuran-2-carboxamide,  
[0614] N-(4-aminobiphenyl-3-yl)-4-(3-hydroxyazetidin-1-yl)benzamide,  
[0615] N-(4-aminobiphenyl-3-yl)-4-(2,3-dihydroxypropylamino)benzamide,  
[0616] N-(4-aminobiphenyl-3-yl)-5-(2-morpholinoethoxy)benzofuran-2-carboxamide,  
[0617] N-(4-amino-4'-fluorobiphenyl-3-yl)-5-(2-morpholinoethoxy)benzofuran-2-carboxamide,  
[0618] N-(4-aminobiphenyl-3-yl)-5-(2-(piperidin-1-yl)ethoxy)benzofuran-2-carboxamide,  
[0619] N-(4-aminobiphenyl-3-yl)imidazo[1,2-a]pyridine-2-carboxamide,  
[0620] N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(2,3-dihydroxypropylamino)benzamide,  
[0621] N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(3-hydroxyazetidin-1-yl)benzamide,  
[0622] N-(4-amino-4'-fluorobiphenyl-3-yl)-5-(2-(piperidin-1-yl)ethoxy)benzofuran-2-carboxamide,  
[0623] (S)-N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(3-hydroxypyrrolidin-1-yl)benzamide,  
[0624] N-(2-amino-5-(pyridin-4-yl)phenyl)imidazo[1,2-a]pyridine-2-carboxamide,  
[0625] N-(4-aminobiphenyl-3-yl)imidazo[2,1-b]thiazole-6-carboxamide,  
[0626] N-(2-amino-5-(pyridin-2-yl)phenyl)-4-methoxybenzamide,  
[0627] 2-(dimethylamino)ethyl 4-(2-amino-5-(pyridin-2-yl)phenyl)phenylcarbamoylphenylcarbamate,  
[0628] N-(2-amino-5-(pyridin-2-yl)phenyl)-4-(morpholinomethyl)benzamide,  
[0629] N-(2-amino-5-(pyridin-4-yl)phenyl)imidazo[2,1-b]thiazole-6-carboxamide,  
[0630] N-(2-amino-5-(pyridin-4-yl)phenyl)-2-((1S,4S)-5-(3-(trifluoromethyl)phenyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidine-5-carboxamide,  
[0631] (S)-N-(2-amino-5-(pyridin-2-yl)phenyl)-4-(3-aminopyrrolidin-1-yl)benzamide,  
[0632] N-(2-amino-5-(pyridin-2-yl)phenyl)-4-(4-methylpiperazin-1-yl)benzamide,  
[0633] N-(4-aminobiphenyl-3-yl)-7-methoxy-5-(morpholinomethyl)benzofuran-2-carboxamide,  
[0634] N-(2-amino-5-(pyridin-2-yl)phenyl)-4-(4-aminopiperidin-1-yl)benzamide,  
[0635] (S)-N-(2-amino-5-(pyridin-2-yl)phenyl)-4-(3-hydroxypyrrolidin-1-yl)benzamide,  
[0636] N-(4-aminobiphenyl-3-yl)pyrazolo[1,5-a]pyridine-2-carboxamide,

[0637] N-(4-amino-4'-fluorobiphenyl-3-yl)-7-methoxy-5-(morpholinomethyl)benzofuran-2-carboxamide and

[0638] N-(4-aminobiphenyl-3-yl)-5-(4-cyanophenyl)benzofuran-2-carboxamide.

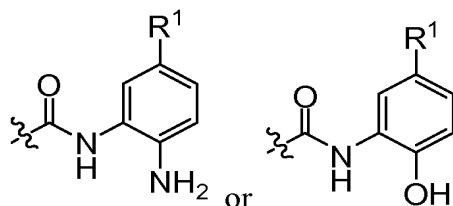
[0639] In the second aspect, the invention provides a composition comprising a compound according to -the present invention together with a pharmaceutically acceptable excipient.

[0640] The third aspect of the invention provides a method of inhibiting histone deacetylase, the method comprising contacting the histone deacetylase with a compound according to -the present invention, or with a composition according to the present invention. Inhibition of the histone deacetylase can be in a cell or a multicellular organism. If in a multicellular organism, the method according to this aspect of the invention comprises administering to the organism a compound according -to the present invention, or a composition according to the present invention. Preferably the organism is a mammal, more preferably a human.

[0641] The data presented herein demonstrate the anti-tumor effects of the HDAC inhibitors of the invention. Recent publications reporting on HDAC inhibitor human clinical trials suggest that these inhibitors can effectively treat human solid tumors or cancer (lung, colon, prostate, stomach, breast, leukemia), including complete remissions of transformed lymphoma (SAHA, ASCO Abstract No. 2321, 2003) and peripheral T-cell lymphoma (depsipeptide/ FR901228 ASCO Abstract No. 88, 2002). Together with the data presented herein demonstrating surprising efficacy at inhibiting HDAC-1 and tumor growth inhibition *in vivo*, these data lead one to reasonably expect that the -inhibitors of the invention are useful not only for inhibition of HDAC, but as therapeutic agents for the treatment of cancer as well.

[0642] All of the compounds in this application were named using Chemdraw Ultra version 9 or 10, which is available through Cambridgesoft.co, 100 Cambridge Park Drive, Cambridge, MA 02140.

[0643] We have unexpectedly found that when HDAC inhibitors including within them the benzamide moiety:



are substituted on the aniline or phenol ring at the 5-position (para to the  $\text{-NH}_2$  or  $\text{-OH}$  group) with a substantially planar ring or ring system (aryl or heteroaryl), the compound's HDAC inhibitory activity (as measured by the human HDAC-1 inhibition assay described below) increases by from 3 to 10 times or more compared to similar compounds in which the aniline or phenol ring is unsubstituted or substituted with a smaller, non-planar moiety, or if the planar moiety is at other than the 5-position of the anilinyll or phenol ring. Additionally, we have found that the planar moiety itself can be substituted. Accordingly,  $\text{R}^1$  in the compounds of the invention is a mono-, bi-, or tri-cyclic aryl or heteroaryl moiety, which moiety is optionally substituted. In some preferred embodiments  $\text{R}^1$  is not further substituted. In other preferred embodiments,  $\text{R}^1$  is substituted with a moiety of from 1-5 atoms, *e.g.*, methyl, hydroxymethyl, halomethyl, halo, hydroxy, amino, etc. In other embodiments,  $\text{R}^1$  is substituted with a larger moiety, *e.g.*, from 6-25 atoms.

[0644] This is surprising in view of T. Suzuki *et. al.*, *J. Med. Chem.*, **1999**, 42, 3001-3003, which teaches that the substitution pattern on the aniline ring of the benzamide fragment of known HDACs (wherein the amino group is ortho to the amide nitrogen) is highly sensitive to substitutions. Substituents such as Me and OMe ortho- or meta- relative to the amino group are detrimental to HDAC inhibitory activity, causing complete loss of HDAC potency. The same type of substituents in the para-position relative to the amino group did not cause significant drop of potency which allowed assuming that only small substituents such as Me, MeO, F, Cl might be tolerated.

[0645] Furthermore, we have surprisingly found that the HDAC inhibitory activity of such compounds (*i.e.*, compounds comprising the chemical moiety of paragraph [0643] and having a substantially planar ring or ring system at the 5-position of the aniline ring) is substantially independent of the identity of the chemical moiety bound to the carbonyl of the amide in paragraph [0643].

[0646] The following are representative examples of the compounds according to the embodiments described above.

### Pharmaceutical Compositions

[0647] In a second aspect, the invention provides pharmaceutical compositions comprising an inhibitor of histone deacetylase according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method

well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

**[0648]** The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, PA, 1990.

**[0649]** As used herein, the term pharmaceutically acceptable salts refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for Example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula  $-NR^+ + Z^-$ , wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamate, mandelate, benzyloate, and diphenylacetate). As used herein, the term "salt" is also meant to encompass complexes, such as with an alkaline metal or an alkaline earth metal.

**[0650]** The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the

above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01–3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

### **Inhibition of Histone Deacetylase**

**[0651]** In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase according to the invention. Because compounds of the invention inhibit histone deacetylase, they are useful research tools for *in vitro* study histone deacetylases and their role in biological processes. In addition, the compounds of the invention selectively inhibit certain isoforms of HDAC.

**[0652]** Measurement of the enzymatic activity of a histone deacetylase can be achieved using known methodologies. For Example, Yoshida et al., J. Biol. Chem., **265**: 17174-17179 (1990), describes the assessment of histone deacetylase enzymatic activity by the detection of acetylated histones in trichostatin A treated cells. Taunton et al., Science, **272**: 408-411 (1996), similarly describes methods to measure histone deacetylase enzymatic activity using endogenous and recombinant HDAC-1.

**[0653]** In some preferred embodiments, the histone deacetylase inhibitor interacts with and reduces the activity of all histone deacetylases in the cell. In some other preferred embodiments according to this aspect of the invention, the histone deacetylase inhibitor interacts with and reduces the activity of fewer than all histone deacetylases in the cell. In certain preferred embodiments, the inhibitor interacts with and reduces the activity of one histone deacetylase (e.g., HDAC-1), but does not interact with or reduce the activities of other histone deacetylases (e.g., HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8). As discussed below, certain particularly preferred histone deacetylase inhibitors are those that interact with, and reduce the enzymatic activity of, a histone deacetylase that is involved in tumorigenesis. Certain other preferred histone deacetylase inhibitors interact with and reduce the enzymatic activity of a fungal histone deacetylase.



**[0654]** Preferably, the method according to the third aspect of the invention causes an inhibition of cell proliferation of the contacted cells. The phrase "inhibiting cell proliferation" is used to denote an ability of an inhibitor of histone deacetylase to retard the growth of cells contacted with the inhibitor as compared to cells not contacted. An assessment of cell proliferation can be made by counting contacted and non-contacted cells using a Coulter Cell Counter (Coulter, Miami, FL) or a hemacytometer. Where the cells are in a solid growth (e.g., a solid tumor or organ), such an assessment of cell proliferation can be made by measuring the growth with calipers and comparing the size of the growth of contacted cells with non-contacted cells.

**[0655]** Preferably, growth of cells contacted with the inhibitor is retarded by at least 50% as compared to growth of non-contacted cells. More preferably, cell proliferation is inhibited by 100% (i.e., the contacted cells do not increase in number). Most preferably, the phrase "inhibiting cell proliferation" includes a reduction in the number or size of contacted cells, as compared to non-contacted cells. Thus, an inhibitor of histone deacetylase according to the invention that inhibits cell proliferation in a contacted cell may induce the contacted cell to undergo growth retardation, to undergo growth arrest, to undergo programmed cell death (i.e., to apoptose), or to undergo necrotic cell death.

**[0656]** The cell proliferation inhibiting ability of the histone deacetylase inhibitors according to the invention allows the synchronization of a population of asynchronously growing cells. For Example, the histone deacetylase inhibitors of the invention may be used to arrest a population of non-neoplastic cells grown in vitro in the G1 or G2 phase of the cell cycle. Such synchronization allows, for Example, the identification of gene and/or gene products expressed during the G1 or G2 phase of the cell cycle. Such synchronization of cultured cells may also be useful for testing the efficacy of a new transfection protocol, where transfection efficiency varies and is dependent upon the particular cell cycle phase of the cell to be transfected. Use of the histone deacetylase inhibitors of the invention allows the synchronization of a population of cells, thereby aiding detection of enhanced transfection efficiency.

**[0657]** In some preferred embodiments, the contacted cell is a neoplastic cell. The term "neoplastic cell" is used to denote a cell that shows aberrant cell growth. Preferably, the aberrant cell growth of a neoplastic cell is increased cell growth. A neoplastic cell may be a hyperplastic cell, a cell that shows a lack of contact inhibition of growth in vitro, a benign tumor cell that is

incapable of metastasis in vivo, or a cancer cell that is capable of metastasis in vivo and that may recur after attempted removal. The term "tumorigenesis" is used to denote the induction of cell proliferation that leads to the development of a neoplastic growth. In some embodiments, the histone deacetylase inhibitor induces cell differentiation in the contacted cell. Thus, a neoplastic cell, when contacted with an inhibitor of histone deacetylase may be induced to differentiate, resulting in the production of a non-neoplastic daughter cell that is phylogenetically more advanced than the contacted cell.

**[0658]** In some preferred embodiments, in neoplastic cells, antitumor activity of an HDAC inhibitor can be assessed by analyzing expression of certain tumor suppressor genes, such as p21<sup>WAF1/Cip1</sup>. HDAC inhibitors induce p21<sup>WAF1/Cip1</sup> expression in human cancer cells, which leads to retardation of cell proliferation.

**[0659]** In some preferred embodiments, the contacted cell is in an animal. Thus, the invention provides a method for treating a cell proliferative disease or condition in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably, the animal is a mammal, more preferably a domesticated mammal. Most preferably, the animal is a human.

**[0660]** The term "cell proliferative disease or condition" is meant to refer to any condition characterized by aberrant cell growth, preferably abnormally increased cellular proliferation. Examples of such cell proliferative diseases or conditions include, but are not limited to, cancer, restenosis, and psoriasis. In particularly preferred embodiments, the invention provides a method for inhibiting neoplastic cell proliferation in an animal comprising administering to an animal having at least one neoplastic cell present in its body a therapeutically effective amount of a histone deacetylase inhibitor of the invention.

**[0661]** It is contemplated that some compounds of the invention have inhibitory activity against a histone deacetylase from a protozoal source. Thus, the invention also provides a method for treating or preventing a protozoal disease or infection, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a protozoal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

**[0662]** The present invention further provides a method for treating a fungal disease or infection comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a fungal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

**[0663]** The term "therapeutically effective amount" is meant to denote an amount which elicits the desired therapeutic effect, for example, a dosage sufficient to cause inhibition of histone deacetylase activity in the cells of the subject, or a dosage sufficient to inhibit cell proliferation or to induce cell differentiation in the subject. The therapeutic effect is dependent upon the disease being treated and the results desired. As such, the therapeutic effect can be a decrease in the severity of symptoms associated with the disease and/or inhibition (partial or complete) of progression of the disease. The amount needed to elicit the therapeutic response can be determined based on the age, health, size and sex of the patient. Optimal amounts can also be determined based on monitoring of the patient's response to treatment. Administration may be by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain particularly preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

**[0664]** When administered systemically, the histone deacetylase inhibitor is preferably administered at a sufficient dosage to attain a blood level of the inhibitor from about 0.01  $\mu\text{M}$  to about 100  $\mu\text{M}$ , more preferably from about 0.05  $\mu\text{M}$  to about 50  $\mu\text{M}$ , still more preferably from about 0.1  $\mu\text{M}$  to about 25  $\mu\text{M}$ , and still yet more preferably from about 0.5  $\mu\text{M}$  to about 25  $\mu\text{M}$ . For localized administration, much lower concentrations than this may be effective, and much higher concentrations may be tolerated. One of skill in the art will appreciate that the dosage of histone deacetylase inhibitor necessary to produce a therapeutic effect may vary considerably depending on the tissue, organ, or the particular animal or patient to be treated.

**[0665]** In certain preferred embodiments of the third aspect of the invention, the method further comprises contacting the cell with an antisense oligonucleotide that inhibits the expression of a histone deacetylase. The combined use of a nucleic acid level inhibitor (e.g., antisense oligonucleotide) and a protein level inhibitor (i.e., inhibitor of histone deacetylase

enzyme activity) results in an improved inhibitory effect, thereby reducing the amounts of the inhibitors required to obtain a given inhibitory effect as compared to the amounts necessary when either is used individually. The antisense oligonucleotides according to this aspect of the invention are complementary to regions of RNA or double-stranded DNA that encode HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, HDAC-9, HDAC-10 and/or HDAC-11 (see e.g., GenBank Accession Number U50079 for HDAC-1, GenBank Accession Number U31814 for HDAC-2, and GenBank Accession Number U75697 for HDAC-3).

**[0666]** For purposes of the invention, the term "oligonucleotide" includes polymers of two or more deoxyribonucleosides, ribonucleosides, or 2'-substituted ribonucleoside residues, or any combination thereof. Preferably, such oligonucleotides have from about 6 to about 100 nucleoside residues, more preferably from about 8 to about 50 nucleoside residues, and most preferably from about 12 to about 30 nucleoside residues. The nucleoside residues may be coupled to each other by any of the numerous known internucleoside linkages. Such internucleoside linkages include without limitation phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate and sulfone internucleoside linkages. In certain preferred embodiments, these internucleoside linkages may be phosphodiester, phosphotriester, phosphorothioate, or phosphoramidate linkages, or combinations thereof. The term oligonucleotide also encompasses such polymers having chemically modified bases or sugars and/or having additional substituents, including without limitation lipophilic groups, intercalating agents, diamines and adamantane.

**[0667]** For purposes of the invention the term "2'-substituted ribonucleoside" includes ribonucleosides in which the hydroxyl group at the 2' position of the pentose moiety is substituted to produce a 2'-O-substituted ribonucleoside. Preferably, such substitution is with a lower alkyl group containing 1-6 saturated or unsaturated carbon atoms, or with an aryl or allyl group having 2-6 carbon atoms, wherein such alkyl, aryl or allyl group may be unsubstituted or may be substituted, e.g., with halo, hydroxy, trifluoromethyl, cyano, nitro, acyl, acyloxy, alkoxy, carboxyl, carbalkoxyl, or amino groups. The term "2'-substituted ribonucleoside" also includes

ribonucleosides in which the 2'-hydroxyl group is replaced with an amino group or with a halo group, preferably fluoro.

**[0668]** Particularly preferred antisense oligonucleotides utilized in this aspect of the invention include chimeric oligonucleotides and hybrid oligonucleotides.

**[0669]** For purposes of the invention, a "chimeric oligonucleotide" refers to an oligonucleotide having more than one type of internucleoside linkage. One preferred Example of such a chimeric oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region, preferably comprising from about 2 to about 12 nucleotides, and an alkylphosphonate or alkylphosphonothioate region (see e.g., Pederson et al. U.S. Patent Nos. 5,635,377 and 5,366,878). Preferably, such chimeric oligonucleotides contain at least three consecutive internucleoside linkages selected from phosphodiester and phosphorothioate linkages, or combinations thereof.

**[0670]** For purposes of the invention, a "hybrid oligonucleotide" refers to an oligonucleotide having more than one type of nucleoside. One preferred Example of such a hybrid oligonucleotide comprises a ribonucleotide or 2'-substituted ribonucleotide region, preferably comprising from about 2 to about 12 2'-substituted nucleotides, and a deoxyribonucleotide region. Preferably, such a hybrid oligonucleotide contains at least three consecutive deoxyribonucleosides and also contains ribonucleosides, 2'-substituted ribonucleosides, preferably 2'-O-substituted ribonucleosides, or combinations thereof (see e.g., Metelev and Agrawal, U.S. Patent No. 5,652,355).

**[0671]** The exact nucleotide sequence and chemical structure of an antisense oligonucleotide utilized in the invention can be varied, so long as the oligonucleotide retains its ability to inhibit expression of the gene of interest. This is readily determined by testing whether the particular antisense oligonucleotide is active. Useful assays for this purpose include quantitating the mRNA encoding a product of the gene, a Western blotting analysis assay for the product of the gene, an activity assay for an enzymatically active gene product, or a soft agar growth assay, or a reporter gene construct assay, or an in vivo tumor growth assay, all of which are described in detail in this specification or in Ramchandani et al. (1997) Proc. Natl. Acad. Sci. USA 94: 684-689.

**[0672]** Antisense oligonucleotides utilized in the invention may conveniently be synthesized on a suitable solid support using well known chemical approaches, including H-phosphonate

chemistry, phosphoramidite chemistry, or a combination of H-phosphonate chemistry and phosphoramidite chemistry (i.e., H-phosphonate chemistry for some cycles and phosphoramidite chemistry for other cycles). Suitable solid supports include any of the standard solid supports used for solid phase oligonucleotide synthesis, such as controlled-pore glass (CPG) (see, e.g., Pon, R.T. (1993) Methods in Molec. Biol. 20: 465-496).

[0673] Particularly preferred oligonucleotides have nucleotide sequences of from about 13 to about 35 nucleotides.. Yet additional particularly preferred oligonucleotides have nucleotide sequences of from about 15 to about 26 nucleotides.

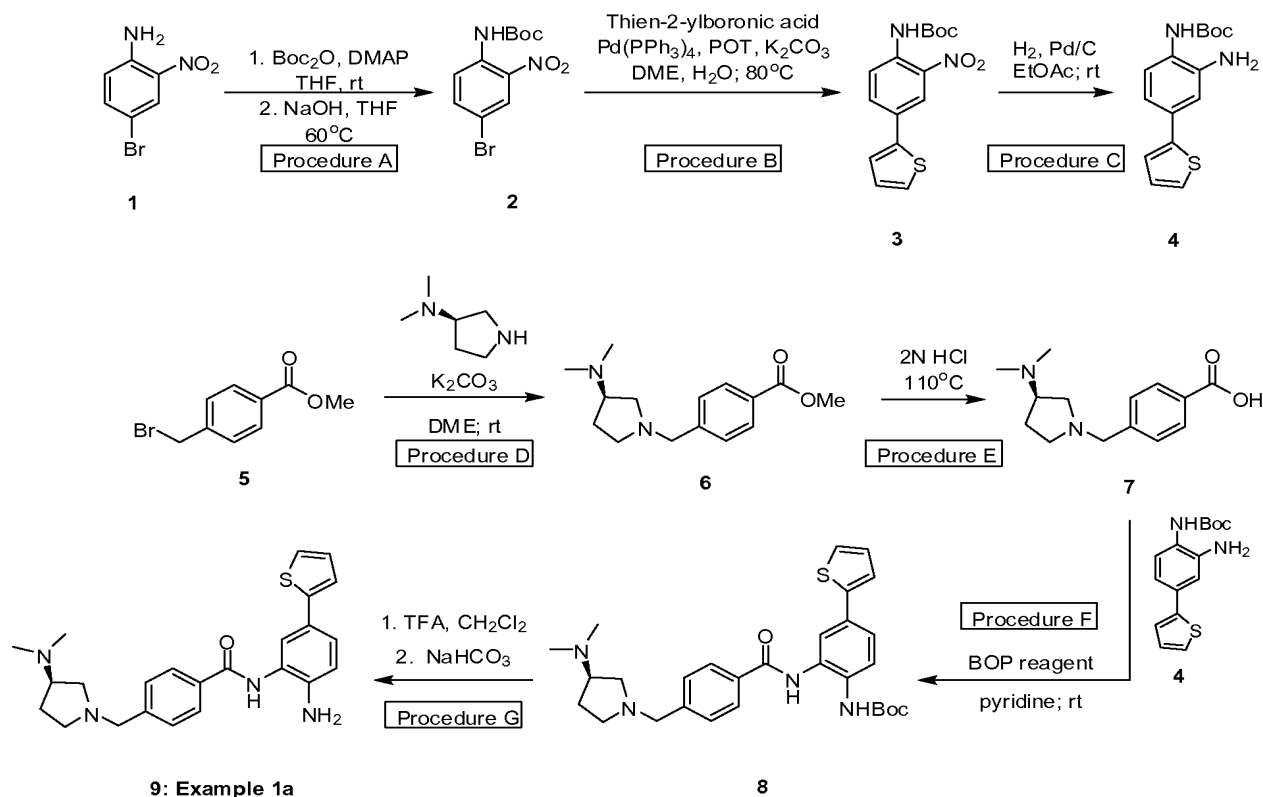
[0674] The following Examples are intended to further illustrate certain preferred embodiments of the invention, and are not intended to limit the scope of the invention.

## EXAMPLES

### Example 1a

**(R)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide (9)**

## Scheme 1

Step 1. *tert*-Butyl 4-bromo-2-nitrophenylcarbamate (2)

[0675] To a solution of 4-bromo-2-nitroaniline **1** (10.0 g; 46.1 mmol) and Boc-anhydride (20.11 g, 92.2 mmol) in THF (100 mL) stirred at room temperature was added a catalytic amount of 4-(dimethylamino)pyridine (DMAP). The reaction mixture was allowed to stir for 90 min, the solvent was removed *in vacuo* and the residue was dried under vacuum to produce colorless oil. The oil was dissolved in THF (46 mL), treated with an aqueous sodium hydroxide solution (2N, 46 mL) and heated to 65 °C for 18 h. Solid sodium hydroxide (1.8 g, 46.1 mmol) was added to the reaction mixture and heating was continued for 4 h; then the THF was removed *in vacuo* and a yellow solid crashed from the aqueous solution. The solid was filtered, washed with H<sub>2</sub>O and dried under vacuum to afford title compound **2** (15 g, >99% yield).

[0676] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.67 (s, 1H), 8.05 (d, J= 2.2 Hz, 1H), 7.78 (dd, J= 8.8, 2.2 Hz, 1H), 7.57 (d, J= 8.8 Hz, 1H), 1.43 (s, 9H).

Step 2: *tert*-Butyl 2-nitro-4-(thiophen-2-yl)phenylcarbamate (3)

[0677] A suspension of 2-thiophene boronic acid (3.93 g, 30.7 mmol), bromoarene **2** (7.31 g, 23.1 mmol), *tri*-*o*-tolyl-phosphine (2.16 g, 7.1 mmol) and potassium carbonate (9.81 g, 70.9 mmol) in degassed ethyleneglycol dimethylether (DME) (120 mL) and H<sub>2</sub>O (40 mL) was treated with tetrakis(triphenylphosphine)palladium(0) (1.78 g, 1.5 mmol). The mixture was stirred in a preheated oil bath at 80 °C for 18 h, diluted with AcOEt (200 mL), washed with brine, dried over MgSO<sub>4</sub> and concentrated. The crude material was either purified by flash chromatography (eluent: 10% AcOEt in hexane) or triturated in a mixture AcOEt: hexane (10:1, 100 mL) to give title compound **3** (6.74 g, 90% yield).

[0678] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 9.63 (s, 1H), 8.12 (d, *J* = 2.3 Hz, 1H), 7.92 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.62 to 7.59 (m, 2H), 7.59 to 7.52 (m, 1H), 7.15 (dd, *J* = 4.9, 3.5 Hz, 1H), 1.45 (s, 9H).

Step 3: *tert*-Butyl 2-amino-4-(thiophen-2-yl)phenylcarbamate (4)

[0679] Compound **3** was suspended in AcOEt and placed under nitrogen atmosphere; then 10% palladium on carbon (catalytic amount) was added. The reaction mixture was placed under vacuum for a few min then opened up under a balloon of hydrogen and stirred at ambient temperature for 18 h. The reaction mixture was filtered through Celite® and concentrated to give compound **4** (0.393 g, 95% yield).

[0680] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 8.33 (s, 1H), 7.42 (dd, *J* = 4.9, 0.98 Hz, 1H), 7.27 (dd, *J* = 3.5, 0.98 Hz, 1H), 7.06 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.95 (d, *J* = 2.2 Hz, 1H), 6.82 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 5.01 (s, 2H), 1.47 (s, 9H).

Step 4: (R)-Methyl 4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzoate (6)

[0681] Methyl 4-(bromomethyl)benzoate **5** (0.5 g, 2.2 mmol), (R)-*N,N*-dimethylpyrrolidin-3-amine (0.523 g, 4.6 mmol) and potassium carbonate (0.392 g, 2.8 mmol) were stirred at room temperature for 18 h in ethyleneglycol dimethylether (3 mL) then diluted with DCM (20 mL), washed with brine, dried over MgSO<sub>4</sub> and concentrated to give title compound **6** (0.57 g, 96% yield).

[0682] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 7.88 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 3.60 (abq, *J* = 44.0, 13.5 Hz, 2H), 2.69 to 2.61 (m, 2H), 2.58 to 2.50 (m, 1H), 2.48 to 2.39 (m, 1H), 2.26 to 2.23 (m, 1H), 2.05 (s, 6H), 1.85 to 1.81 (m, 1H), 1.62 to 1.56 (m, 1H).



Step 5: (R)-4-((3-(Dimethylamino)pyrrolidin-1-yl)methyl)benzoic acid (7)

[0683] Compound **6** (0.55 g, 2.1 mmol) was heated to 110 °C in 2N aqueous hydrochloric acid (7 mL) for 18 h then cooled to -78 °C and lyophilized to give compound **7** as a grey solid (0.65 g, 97% yield). LRMS: 248.2 (calc), 249.0 (obs).

Step 6: (R)-tert-Butyl 2-(4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamido)-4-(thiophen-2-yl)phenylcarbamate (8)

[0684] A solution of acid **7** (0.20 g, .62 mmol), amine **4** (0.164 g, 0.56 mmol) and BOP reagent (0.30 g, 0.68 mmol) in pyridine (4 mL) was stirred for 18 h, concentrated, diluted with AcOEt, washed with aqueous sodium bicarbonate (NaHCO<sub>3</sub>), brine, dried over MgSO<sub>4</sub>, filtered and concentrated. Flash chromatography purification of the residue (eluent: 1:1 MeOH: AcOEt with 1% triethylamine) gave compound **8** (0.198 g, 67% yield).

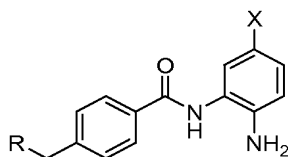
[0685] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.86 (s, 1H), 8.72 (s, 1H), 7.92 (d, J= 8.2 Hz, 2H), 7.79 (d, J= 2.0 Hz, 1H), 7.59 (d, J= 8.6 Hz, 1H), 7.51 (d, J= 1.2 Hz, 1H), 7.50 (d, J= 1.2 Hz, 1H), 7.46 to 7.43 (m, 3H), 7.11 (dd, J= 5.1, 3.5 Hz, 1H), 3.64 (abq, J= 40.5, 13.3 Hz, 2H), 2.84 to 2.75 (m, 1H), 2.67 to 2.63 (m, 1H), 2.33 (m, 2H), 2.13 (s, 6H), 1.99 to 1.88 (m, 1H), 1.66 (m, 1H), 1.45 (s, 9H), 1.25 (m, 1H).

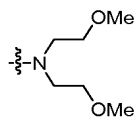

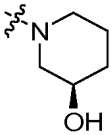

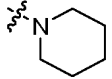

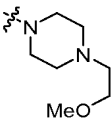



Step 7: (R)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide (9)

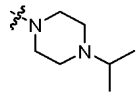

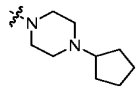

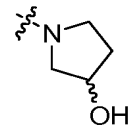

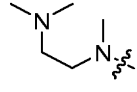

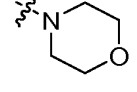

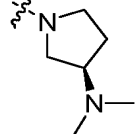

[0686] To a solution of compound **8** (0.198 g, 0.38 mmol) in DCM (3 mL) was added neat trifluoroacetic acid (1 mL). The solution was allowed to stir at room temperature for 90 min, concentrated (without heating), taken up in AcOEt, washed with saturated aqueous NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give title compound **9** (0.038 g, 24% yield).

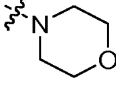
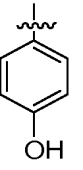
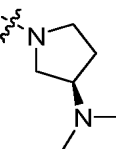
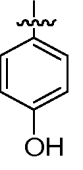
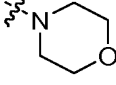
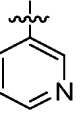
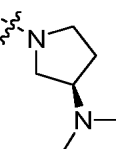
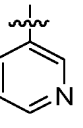
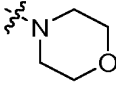
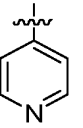
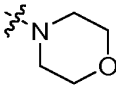

[0687] <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ (ppm) 9.69 (s, 1H), 7.94 (s, J= 7.8 Hz, 2H), 7.43 (t, J= 8.0 Hz, 3H), 7.34 (d, J= 5.1 Hz, 1H), 7.28 (dd, J= 8.2, 2.0 Hz, 1H), 7.22 (d, J= 3.3 Hz, 1H), 7.03 (t, J= 3.5 Hz, 1H), 6.79 (d, J= 8.4 Hz, 1H), 5.15 (s, 2H), 3.63 (q, J= 36.8, 14.1 Hz, 2H), 2.67 to 2.63 (m, 1H), 2.45-2.37 (m, 2H), 2.33 to 2.19 (m, 7H), 1.90 (m, 2H), 1.68 (m, 1H).

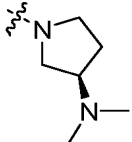

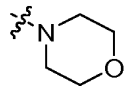

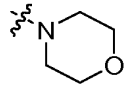

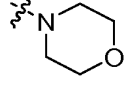

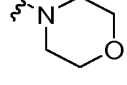

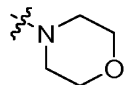
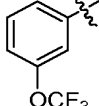
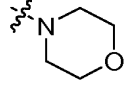

Table 1: Characterization of compounds prepared according to Scheme 1



Cpd	Ex	R	X	Name	Characterization
10	1b			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((bis(2-methoxyethyl)amino)methyl)-benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.69 (s, 1H), 7.93 (d, J= 8.2 Hz, 2H), 7.45 (s, 1H), 7.43 (d, J= 8.4 Hz, 2H), 7.34 (dd, J= 5.1, 1.2 Hz, 1H), 7.28 (dd, J= 8.2, 2.2 Hz, 1H), 7.22 (dd, J= 3.5, 1.2 Hz, 1H), 7.03 (dd, J= 5.1, 3.5 Hz, 1H), 6.79 (d, J= 8.4 Hz, 1H), 5.14 (s, 2H), 3.71 (s, 2H), 3.40 (t, J= 6.1 Hz, 4H), 3.20 (s, 6H), 2.63 (t, J= 6.1 Hz, 4H). LRMS: 439.19 (calc) 440.2 (obs).
11	1c			(R)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-hydroxypiperidin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.69 (s, 1H), 7.94 (d, J= 8.2 Hz, 2H), 7.45 (d, J= 2.2 Hz, 1H), 7.41 (d, J= 8.2 Hz, 2H), 7.34 (dd, J= 5.1, 0.98 Hz, 1H), 7.28 (dd, J= 8.4, 2.2 Hz, 1H), 7.22 (dd, J= 3.7, 1.2 Hz, 1H), 7.03 (dd, J= 5.1, 3.5 Hz, 1H), 6.79 (d, J= 8.4 Hz, 1H), 5.14 (s, 2H), 4.59 (d, J= 5.1 Hz, 1H), 3.52 (abq, J= 36.8, 13.3 Hz, 2H), 3.44 to 3.43 (m, 1H), 2.76 (d, J= 10.4 Hz, 1H), 2.63 (d, J= 11.3 Hz, 1H), 1.87 to 1.69 (m, 3H), 1.62 to 1.58 (m, 1H), 1.45 to 1.39 (m, 1H), 1.06 to 1.04 (m, 1H). LRMS: 407.17 (calc) 408.0 (obs).
12	1d			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(piperidin-1-ylmethyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.87, (s, 1H), 9.34 (s, 1H), 8.07 (d, J= 8.2 Hz, 2H), 7.62 (d, J= 7.8 Hz, 2H), 7.46 (s, 1H), 7.36 (s, J= 5.1 Hz, 1H), 7.33 (d, J= 8.4 Hz, 1H), 7.25 (d, J= 3.5 Hz, 1H), 7.04 (dd, J= 5.1, 3.5 Hz, 1H), 6.86 (d, J= 8.2 Hz, 1H), 4.36 (d, J= 5.1 Hz, 2H), 3.39 to 3.31 (m, 2H), 2.93 to 2.86 (m, 2H), 1.83 (d, J= 14.1 Hz, 2H), 1.71 to 1.57 (m, 3H), 1.38 to 1.34 (m, 1H). LRMS: 391.17 (calc) 392.1 (obs).
13	1e			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-(2-methoxyethyl)piperazin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.70 (s, 1H), 7.94 (d, J= 8.2 Hz, 2H), 7.45 (d, J= 2.0 Hz, 1H), 7.41 (d, J= 8.2 Hz, 2H), 7.34 (dd, J= 5.1, 0.98 Hz, 1H), 7.28 (dd, J= 8.2, 2.2 Hz, 1H), 7.22 (dd, J= 3.5, 0.98 Hz, 1H), 7.03 (dd, J= 5.1, 3.7 Hz, 1H), 6.79 (d, J= 8.4 Hz, 1H), 5.14 (s, 2H), 3.52 (s, 2H), 3.40 (t, J= 5.8 Hz, 3H), 3.20 (s, 3H), 2.38 (m, 9H). LRMS: 450.21 (calc) 451.1 (obs).
14	1f			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((ethyl(methyl)amino)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.71, (s, 1H), 7.95 (d, J= 7.8 Hz, 2H), 7.45 to 7.42 (m, 4H), 7.34 (d, J= 4.1 Hz, 1H), 7.28 (dd, J= 8.2, 2.2 Hz, 1H), 7.23 (d, J= 2.5 Hz, 1H), 7.03 (dd, J= 5.1, 3.5 Hz, 1H), 6.79 (d, J= 8.2 Hz, 1H), 5.14 (s, 2H), 3.53 (m, 2H), 2.40 (m, 2H), 2.13 (s, 3H), 1.03 (t, J= 7.0 Hz, 3H). LRMS: 365.16 (calc) 366.0 (obs).

Cpd	Ex	R	X	Name	Characterization
15	1g			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-isopropylpiperazin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.70 (s, 1H), 7.49 (d, J= 8.0 Hz, 2H), 7.45 (d, J= 2.2 Hz, 1H), 7.42 (d, J= 8.2 Hz, 2H), 7.34 (dd, J= 5.1, 1.2 Hz, 1H), 7.28 (dd, J= 8.4, 2.2 Hz, 1H), 7.22 (dd, J= 3.5, 1.2 Hz, 1H), 7.03 (dd, J= 5.1, 3.5 Hz, 1H), 6.79 (d, J= 8.4 Hz, 1H), 5.14 (s, 2H), 3.53 (s, 2H), 2.65 (m, 1H), 2.31 to 1.97 (m, 8H), 0.98 (m, 6H). LRMS: 434.60 (calc) 435.1 (obs).
16	1h			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-cyclopentylpiperazin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.70 (s, 1H), 7.95 (d, J= 7.8 Hz, 2H), 7.44 (d, J= 4.3 Hz, 2H), 7.41 (s, 1H), 7.34 (d, J= 5.1 Hz, 1H), 7.28 (dd, J= 8.4, 2.0 Hz, 1H), 7.22 (d, J= 3.1 Hz, 1H), 6.79 (d, J= 8.4 Hz, 1H), 5.14 (s, 2H), 3.55 (s, 2H), 2.31 (m, 9H), 1.80 (m, 2H), 1.60 (m, 2H), 1.48 (m, 2H), 1.35 (m, 2H). LRMS: 460.23 (calc) 461.1 (obs).
17	1i			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-hydroxypyrrolidin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.69 (s, 1H), 7.93 (m, 2H), 7.42 (t, J= 9.2 Hz, 3H), 7.34 (dd, J= 5.1, 1.2 Hz, 1H), 7.28 (dd, J= 8.4, 2.3 Hz, 1H), 7.22 (m, 1H), 7.03 (dd, J= 5.1, 3.5 Hz, 1H), 6.79 (d, J= 8.4 Hz, 1H), 5.15 (s, 2H), 4.70 (d, J= 4.5 Hz, 1H), 4.19 (m, 1H), 3.62 (q, J= 23.7, 13.3 Hz, 2H), 2.68 (m, 1H), 2.57 (m, 1H), 2.39 (m, 1H), 2.30 (m, 1H), 2.01 (m, 1H), 1.55 (m, 1H). LRMS: 393.15 (calc) 394.1 (obs).
18	1j			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)benzamide	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 7.97 (d, J=8.2 Hz, 2H), 7.50 (d, J=8.5 Hz, 2H), 7.49 (d, J=2.2 Hz, 1H), 7.35 (dd, J=8.4, 2.2 Hz, 1H), 7.23 (dd, J=5.1, 1.0 Hz, 1H), 7.21 (dd, J=3.5, 1.0 Hz, 1H), 7.01 (dd, J=5.1, 3.7 Hz, 1H), 6.91 (d, J=8.4 Hz, 1H), 3.62 (s, 2H), 2.62-2.55 (m, 8H), 2.30 (s, 6H), 2.25 (s, 3H). LRMS: 408.57 (calc) 409.2 (obs).
19	1k			N-(4-aminobiphenyl-3-yl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 7.97 (d, 2H, J=8.2Hz), 7.57-7.48 (mult, 5H), 7.37 (t, 3H, J=2.2Hz), 7.24 (td, 1H, J=1.2 & 7.2 Hz), 6.97 (d, 1H, J=8.2Hz), 3.71 (t, 4H, J=4.3Hz), 3.62 (s, 2H), 2.50 (s, 4H). LRMS: 387.47 (calc) 388.3 and 194.8 (obs).
20	1l			(R)-N-(4-aminobiphenyl-3-yl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.70 (s, 1H), 7.94 (d, J= 8.0 Hz, 2H), 7.54 (d, J= 7.2 Hz, 2H), 7.50 (s, 1H), 7.43 to 7.35 (m, 4H), 7.31 (dd, J= 8.4, 2.2 Hz, 1H), 7.22 (t, J= 7.3 Hz, 1H), 6.85 (d, J= 8.4 Hz, 1H), 5.08 (s, 2H), 3.61 (abq, J= 41.9, 13.3 Hz, 2H), 2.65 to 2.53 (m, 2H), 2.43 (m, 1H), 2.31 (m, 1H), 2.07 (s, 6H), 1.89 to 1.84 (m, 1H), 1.61 (m, 1H), 1.21 (m, 1H). LRMS: 414.24 (calc), 415.2 (obs).

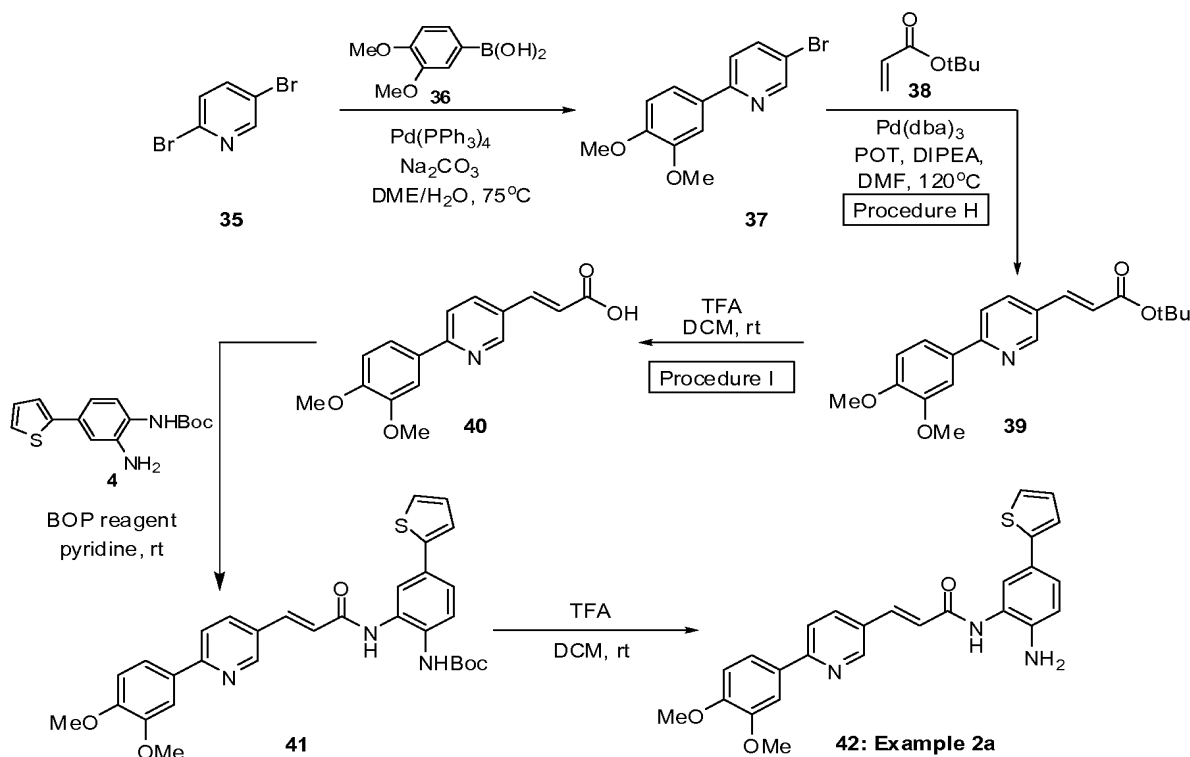
Cpd	Ex	R	X	Name	Characterization
21	1m			N-(4-amino-4'-hydroxybiphenyl-3-yl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.69 (s, 1H), 9.33 (s, 1H), 7.95 (d, J= 8.0 Hz, 2H), 7.43 (d, J= 8.2 Hz, 2H), 7.38 (d, J= 2.0 Hz, 1H), 7.33 (d, J= 8.4 Hz, 2H), 7.20 (dd, J= 8.2, 2.2 Hz, 1H), 6.80 (d, J= 8.2 Hz, 1H), 6.76 (d, J= 8.8 Hz, 2H), 4.94 (s, 2H), 3.60 (t, J= 4.5 Hz, 4H), 3.53 (s, 2H), 2.47 to 2.35 (m, 4H). LRMS: 403.19 (calc) 404.1 (obs).
22	1n			(R)-N-(4-amino-4'-hydroxybiphenyl-3-yl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.68 (s, 1H), 9.33 (s, 1H), 7.93 (d, J= 8.2 Hz, 2H), 7.41 (d, J= 8.2 Hz, 2H), 7.34 (s, 1H), 7.33 (d, J= 8.4 Hz, 2H), 7.20 (dd, J= 8.2, 2.2 Hz, 1H), 6.80 (d, J= 8.4 Hz, 1H), 6.76 (d, J= 8.6 Hz, 2H), 4.94 (s, 2H), 3.61 (abq, J= 40.5, 13.1 Hz, 2H), 2.65 to 2.61 (m, 2H), 2.57 to 2.53 (m, 2H), 2.31 (m, 2H), 2.09 (s, 6H), 1.97 to 1.86 (m, 1H). LRMS: 430.24 (calc) 431.2 (obs).
23	1o			N-(2-amino-5-(pyridin-3-yl)phenyl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.72 (s, 1H), 8.77 (d, J= 2.2 Hz, 1H), 8.42 (dd, J= 4.7, 1.4 Hz, 1H), 7.96 (d, J= 8.2 Hz, 2H), 7.92 (dt, J= 8.2, 2.2 Hz, 1H), 7.55 (d, J= 2.2 Hz, 1H), 7.44 (d, J= 8.0 Hz, 2H), 7.38 (dt, J= 7.4, 2.5 Hz, 2H), 6.88 (d, J= 8.2 Hz, 1H), 5.20 (s, 2H), 3.57 (t, J= 4.4 Hz, 4H), 3.53 (s, 2H), 2.35 (m, 4H). LRMS: 388.19 (calc) 389.0 (obs).
24	1p			(R)-N-(2-amino-5-(pyridin-3-yl)phenyl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.94 (s, 1H), 9.82 (s, 1H), 8.88 (s, 1H), 8.52 (d, J= 5.1 Hz, 1H), 8.05 (d, J= 7.6 Hz, 2H), 7.60 (s, 2H), 7.58 (d, J= 5.1 Hz, 2H), 7.46 (dd, J= 8.4, 2.3 Hz, 1H), 6.91 (d, J= 8.4 Hz, 1H), 3.92 (m, 2H), 2.78 (s, 6H), 2.65 (m, 2H), 2.53 to 2.51 (m, 2H), 2.43 (m, 1H), 2.31 to 2.30 (m, 2H). LRMS: 415.24 (calc) 416.2 (obs).
25	1q			N-(2-amino-5-(pyridin-4-yl)phenyl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.73 (s, 1H), 8.51 (dd, J= 4.7, 1.6 Hz, 2H), 7.98 (d, J= 8.0 Hz, 2H), 7.68 (d, J= 2.0 Hz, 1H), 7.58 (dd, J= 4.5, 1.6 Hz, 2H), 7.51 (dd, J= 8.4, 2.2 Hz, 1H), 7.46 (d, J= 8.2 Hz, 2H), 6.88 (d, J= 8.4 Hz, 1H), 5.39 (s, 2H), 3.59 (t, J= 4.4 Hz, 4H), 3.55 (s, 2H), 2.37 (m, 4H). LRMS: 388.2 (calc) 389.1 (obs).
26	1r			N-(2-amino-5-(thiophen-3-yl)phenyl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.74 (s, 1H), 7.97 (d, J= 8.0 Hz, 2H), 7.58 to 7.57 (m, 1H), 7.56 (t, J= 2.0 Hz, 1H), 7.51 (d, J= 2.0 Hz, 1H), 7.45 (d, J= 8.2 Hz, 2H), 7.42 (dd, J= 4.9 Hz, 1H), 7.36 (dd, J= 8.4, 2.2 Hz, 1H), 6.81 (d, J= 8.4 Hz, 1H), 5.04 (s, 2H), 3.59 (t, J= 4.5 Hz, 4H), 3.55 (s, 2H), 2.37 (m, 4H). LRMS: 393.2 (calc) 394.1 (obs)

Cpd	Ex	R	X	Name	Characterization
27	1s			(R)-N-(2-amino-5-(thiophen-3-yl)phenyl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.72 (s, 1H), 7.96 (d, J= 8.2 Hz, 2H), 7.58 to 7.55 (m, 2H), 7.51 (d, J= 2.0 Hz, 1H), 7.44 (s, 1H), 7.43 to 7.41 (m, 2H), 7.36 (dd, J= 8.4, 2.2 Hz, 1H), 6.81 (d, J= 8.4 Hz, 1H), 5.04 (s, 2H), 3.62 (abq, J= 42.6, 13.5 Hz, 2H), 2.73 (m, 1H), 2.67 to 2.63 (m, 1H), 2.61 to 2.55 (m, 1H), 2.47 to 2.43 (m, 1H), 2.30 to 2.26 (m, 1H), 2.09 (s, 6H), 1.92 to 1.82 (m, 1H), 1.66 to 1.58 (m, 1H). LRMS: 420.2 (calc) 421.1 (obs)
28	1t			N-(2-amino-5-(6-fluoropyridin-3-yl)phenyl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 8.34 (s, 1H), 7.92 (m, 1H), 7.88 (d, J=9.0 Hz, 2H), 7.57 (s, 1H), 7.43 (d, J=9.1 Hz, 2H), 7.24 (m, 1H), 6.92 (m, 2H), 4.01 (s, 2H), 3.72 (t, J=4.5 Hz, 5H), 3.58 (s, 1H) 2.43 (m, 5H). LRMS: 406.45 (calc) 407.1 (obs)
29	1u			N-(2-amino-5-(5-cyanothiophen-2-yl)phenyl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 7.92 (s, 1H), 7.82 (d, J=8.1 Hz, 2H), 7.51 (s, 1H), 7.42 (d, J=3.9 Hz, 1H), 7.41 (d, J=8.0 Hz, 2H), 7.28 (m, 1H), 7.07 (d, J=4.1 Hz, 1H), 6.31 (d, J=8.41 Hz, 1H), 4.09 (m, 2H), 3.62 (m, 4H), 2.39 (m, 4H). LRMS: 418.51 (calc) 419.2 (obs)
30	1v			N-(2-amino-5-(benzo[d][1,3]dioxol-5-yl)phenyl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 7.89 (m, 2H), 7.42 (m, 2H), 7.21 (m, 1H), 7.01 (m, 2H), 6.82 (dd, J=20.0, 8.2 Hz, 2H), 6.01 (s, 2H), 3.98 (s, 2H), 3.78 (t, J=4.2 Hz, 4H), 3.59 (s, 2H), 2.42 (m, 4H), 1.61 (s, 1H). LRMS: 431.48 (calc) 432.2 (obs).
31	1w			N-(2-amino-5-(5-methylthiophen-2-yl)phenyl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 8.15 (s, 1H), 7.84 (d, J=8.1 Hz, 2H), 7.44 (s, 1H), 7.40 (d, J=8.0 Hz, 2H), 7.24 (m, 1H), 6.93 (d, J=3.5 Hz, 1H), 6.78 (d, J=8.0 Hz, 2H), 6.67 (m, 1H), 4.01 (m, 2H), 3.71 (t, J=5.0 Hz, 4H), 3.53 (s, 2H), 2.48 (s, 3H), 2.43 (m, 3H). LRMS: 407.17 (calc) 408.1 (obs).
32	1x			N-(4-amino-5'-(trifluoromethoxy)biphenyl-3-yl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 7.91 (d, J=8.0 Hz, 2H), 7.57 (s, 1H), 7.48 (m, 2H), 7.37 (m, 2H), 7.13 (m, 1H), 6.92 (d, J=8.0 Hz, 1H), 4.01 (s, 2H), 3.71 (t, J=4.1 Hz, 4H), 3.57 (s, 2H), 2.48 (m, 3H), 1.61 (s, 1H). LRMS: 471.47(calc) 472.2 (obs).
33	1y			(E)-N-(2-amino-5-(3-methoxyprop-1-enyl)phenyl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 7.89 to 7.84 (m, 3H), 7.46 (d, J= 8.2 Hz, 2H), 7.33 (s, 1H), 7.15 (dd, J= 8.2, 2.0 Hz, 1H), 6.78 (d, J= 8.2 Hz, 1H), 6.48 (d, J= 15.8 Hz, 1H), 6.11 (m, 1H), 4.04 (dd, J= 6.3, 1.4 Hz, 2H), 3.82 (bs, 2H), 3.72 (t, J= 4.6 Hz, 4H), 3.56 (s, 2H), 3.36 (s, 3H), 2.45 (t, J= 4.5 Hz, 4H). LRMS: 381.2 (calc) 381.2 (obs).

## Example 2a

## (E)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-3-(6-(3,4-dimethoxyphenyl)pyridin-3-yl)acrylamide (42)

## Scheme 2

Step 1: 5-Bromo-2-(3,4-dimethoxyphenyl)pyridine (37)

[0688] To a degassed solution of 2,5-dibromopyridine **35** (0.50 g, 2.11 mmol), 3,4-dimethoxyphenylboronic acid **36** (0.50 g, 2.74 mmol) and sodium carbonate (0.67 g, 6.3 mmol) in ethyleneglycol dimethylether (7 mL) and H<sub>2</sub>O (2 mL) was added tetrakis(triphenylphosphine)-palladium(0) (0.16 g, 0.14 mmol) and the solution was stirred at 75 °C for 18 h. The reaction mixture was filtered, concentrated, diluted with AcOEt, washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. Flash chromatography of the residue (eluent: 3:1 hexane: AcOEt) provided title compound **37** (0.47 g, 76% yield).

[0689] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 8.70 (d, J= 2.3 Hz, 1H), 8.04 (dd, J= 8.6, 2.5 Hz, 1H), 7.91 (d, J= 8.6 Hz, 1H), 7.65 to 7.61 (m, 2H), 7.04 (d, J= 8.2 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H).

Step 2: (E)-tert-Butyl 3-(6-(3,4-dimethoxyphenyl)pyridin-3-yl)acrylate (39)

[0690] To a degassed solution of bromide **37** (0.47 g, 1.6 mmol), *tert*-butyl acrylate **38** (1.12 mL, 7.7 mmol), POT (0.34 g, 1.1 mmol) and Hunig's base (1.11 mL, 6.4 mmol) in DMF (8 mL) was added tris(dibenzylideneacetone)dipalladium (0) (0.124 g, 0.16 mmol). The solution was placed in a preheated oil bath at 120 °C, stirred for 18 h and concentrated. Flash chromatography purification of the residue (eluent: 3:1 hexane: AcOEt) afforded title compound **39** (0.45 g, 83% yield).

[0691] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 8.84 (d, J= 2.0 Hz, 1H), 8.19 (dd, J= 8.4, 2.2 Hz, 1H), 7.98 (d, J= 8.6 Hz, 1H), 7.72 to 7.69 (m, 2H), 7.59 (d, J= 8.2 Hz, 1H), 7.05 (d, J= 8.2 Hz, 1H), 6.67 (d, J= 16.0 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H).

Step 3: (E)-3-(6-(3,4-Dimethoxyphenyl)pyridin-3-yl)acrylic acid compound with 2,2,2-trifluoroacetic acid (1:1) (40)

[0692] To a solution of *tert*-butyl ester **39** (0.45 g, 1.3 mmol) in DCM (5 mL) was added neat trifluoroacetic acid (1.7 mL). The reaction was allowed to stir at room temperature for 18 h then concentrated; the residue was triturated with diethyl ether, to give title compound **40** (0.376 g, 92% yield).

[0693] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 8.86 (s, 1H), 8.22 (d, J= 8.4 Hz, 1H), 8.01 (d, J= 8.4 Hz, 1H), 7.72 (d, J= 2.0 Hz, 1H), 7.70 (d, J= 2.0 Hz, 1H), 7.64 (d, J= 15.8 Hz, 1H), 7.06 (d, J= 8.2 Hz, 1H), 6.69 (d, J= 16.0 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H).

Step 4: (E)-tert-butyl 2-(3-(6-(3,4-dimethoxyphenyl)pyridin-3-yl)acrylamido)-4-(thiophen-2-yl)phenylcarbamate (41)

[0694] A solution of acid **40** (0.10 g, 0.25 mmol), amine **4** (72.7 mg, 0.25 mmol) and BOP reagent (0.133 g, 3.0 mmol) in pyridine (2 mL) was stirred 18 h at room temperature. The reaction mixture was concentrated and the residue was purified by flash chromatography (eluent: 1:1 hexane: AcOEt) to give title compound **41** (0.14 g, 61% yield).

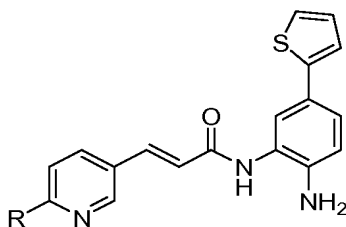
[0695] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.82 (s, 1H), 8.85 (s, 1H), 8.61 (s, 1H), 8.05 (t, J= 12.9 Hz, 2H), 7.89 (s, 1H), 7.75 to 7.73 (m, 2H), 7.70 (d, J= 5.9 Hz, 1H), 7.66 (m, 1H), 7.51 (dd, J= 5.1, 1.2 Hz, 1H), 7.48 to 7.46 (m, 1H), 7.42 (dd, J= 3.7, 1.2 Hz, 1H), 7.12 (dd, J= 5.1, 3.5 Hz, 1H), 7.07 (d, J= 8.4 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 1.48 (s, 9H).

Step 5: (E)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-3-(6-(3,4-dimethoxyphenyl)pyridin-3-yl)acrylamide (42)

**[0696]** To a solution of compound 41 (85.2 mg, 0.15 mmol) in DCM (2 mL) was added neat trifluoroacetic acid (0.7 mL). The reaction was allowed to stir at room temperature for 2 h then concentrated, diluted with AcOEt, washed with saturated aqueous NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give title compound 42 (38 mg, 54% yield).

**[0697]** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.51 (s, 1H), 8.83 (s, 1H), 8.05 (s, J= 2.3 Hz, 2H), 7.74 (s, 1H), 7.71 (d, J= 8.4 Hz, 1H), 7.66 (d, J= 9.8 Hz, 1H), 7.61 (s, 1H), 7.35 (dd, J= 5.1, 1.2 Hz, 1H), 7.24 (dd, J= 8.4, 2.2 Hz, 1H), 7.21 (dd, J= 3.5, 1.2 Hz, 1H), 7.08 to 7.02 (m, 2H), 6.98 (s, 1H), 6.77 (d, J= 8.2 Hz, 1H), 5.22 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H).

Table 2: Characterization of compounds prepared according to Scheme 2



Cpd	Ex	R	Name	Characterization
43	2b		(E)-N-(2-amino-5-(thiophen-2-yl)phenyl)-3-(6-(3,4,5-trimethoxyphenyl)pyridin-3-yl)acrylamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.52 (s, 1H), 8.86 (s, 1H), 8.11 (d, J= 3.1 Hz, 2H), 7.67 (d, J= 2.3 Hz, 1H), 7.63 (s, 1H), 7.45 (s, 2H), 7.35 (dd, J= 5.1, 1.2 Hz, 1H), 7.26 to 7.23 (m, 1H), 7.21 (dd, J= 3.5, 1.2 Hz, 1H), 7.05 to 7.00 (m, 2H), 6.78 (d, J= 8.4 Hz, 1H), 5.22 (s, 2H), 3.89 (s, 6H), 3.72 (s, 3H). LRMS: 487.16 (calc) 488.3 (obs).
44	2c		(E)-3-(2,3'-bipyridin-5-yl)-N-(2-amino-5-(thiophen-2-yl)phenyl)acrylamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.54 (s, 1H), 9.30 (s, 1H), 8.94 (s, 1H), 8.64 (dd, J= 4.7, 1.6 Hz, 1H), 8.48 (d, J= 8.8 Hz, 1H), 8.16 (s, 2H), 7.68 (t, J= 3.3 Hz, 1H), 7.65 (s, 1H), 7.54 (dd, J= 8.2, 4.8 Hz, 1H), 7.35 (dd, J= 4.9, 0.98 Hz, 1H), 7.26 to 7.24 (m, 1H), 7.22 (dd, J= 3.5, 1.2 Hz, 1H), 7.08 (s, 1H), 7.04 (t, J= 3.5 Hz, 1H), 6.78 (d, J= 8.4 Hz, 1H). LRMS: 398.12 (calc) 399.2 (obs).

#### Example 3a

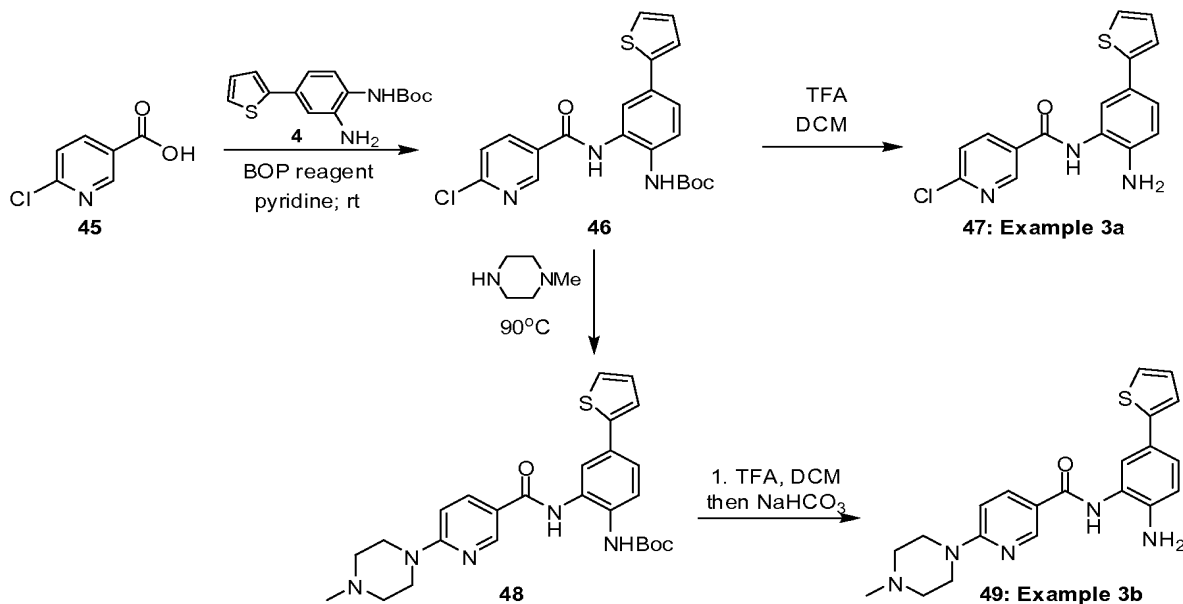
#### N-(2-amino-5-(thiophen-2-yl)phenyl)-6-chloronicotinamide (47)

#### Example 3b

#### N-(2-amino-5-(thiophen-2-yl)phenyl)-6-(4-methylpiperazin-1-yl)nicotinamide (49)



## Scheme 3



Step 1: *tert*-Butyl 2-(6-chloronicotinamido)-4-(thiophen-2-yl)phenylcarbamate (**46**)

[0698] Following the same procedure as described in Example **1a**, step 6 (scheme 1) but substituting compound **7** for compound **45**, title compound **46** was obtained (75% yield).

[0699] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ ppm: 10.08 (s, 1H), 8.97 (d, *J* = 2.3 Hz, 1H), 8.80 (s, 1H), 8.36 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.75 to 7.68 (m, 3H), 7.52 (dd, *J* = 6.1, 2.2 Hz, 1H), 7.51 (t, *J* = 2.5 Hz, 1H), 7.44 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.11 (dd, *J* = 5.1, 3.7 Hz, 1H), 1.44 (s, 9H).

Step 2: *N*-(2-Amino-5-(thiophen-2-yl)phenyl)-6-chloronicotinamide (**47**)

[0700] Following the same procedure as described in Example **1a**, step 7 (scheme 1), but substituting compound **8** for compound **46**, the title compound **47** was obtained (21% yield).

[0701] <sup>1</sup>H NMR: (DMSO-*d*<sub>6</sub>) δ (ppm): 9.91 (s, 1H), 8.97 (d, *J* = 2.2 Hz, 1H), 8.36 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.43 (s, 1H), 7.33 (d, *J* = 5.1 Hz, 1H), 7.29 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.22 (d, *J* = 3.3 Hz, 1H), 7.03 (t, *J* = 3.7 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.28 (s, 2H).

Step 3: *tert*-Butyl 2-(6-(4-methylpiperazin-1-yl)nicotinamido)-4-(thiophen-2-yl)phenylcarbamate (**48**)

[0702] A mixture of chloride **46** (0.15 g, 0.35 mmol) and *N*-methylpiperazine (0.5 mL, 4.5 mmol) was heated to 90 °C in a sealed tube for 18 h. The reaction mixture was then diluted with AcOEt, washed with saturated aqueous NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, filtered and

concentrated. The residue was purified by flash chromatography (eluent: 2:1 AcOEt: hexane) to afford title compound **48** (65 mg, 38% yield).

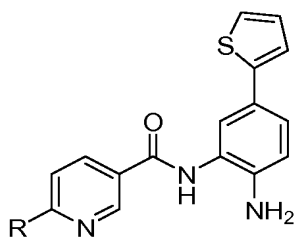
[0703]  $^1\text{H}$  NMR: (DMSO- $d_6$ )  $\delta$  (ppm): 9.71 (s, 1H), 8.72 (s, 1H), 8.65 (s, 1H), 8.04 (d,  $J$ = 8.8 Hz, 1H), 7.76 (s, 1H), 7.60 (d,  $J$ = 8.6 Hz, 1H), 7.51 to 7.46 (m, 2H), 7.43 (d,  $J$ = 3.5 Hz, 1H), 7.11 (t,  $J$ = 3.7 Hz, 1H), 6.93 (d,  $J$ = 8.8 Hz, 1H), 3.64 (s, 3H), 2.39 (m, 4H), 2.22 (m, 4H), 1.46 (s, 9H).

Step 4: *N*-(2-Amino-5-(thiophen-2-yl)phenyl)-6-(4-methylpiperazin-1-yl)nicotinamide (**49**)

[0704] Following the same procedure as described in Example **1a**, Step 7, but substituting compound **8** for compound **48**, the title compound **49** was obtained (19% yield).

[0705]  $^1\text{H}$  NMR: (DMSO- $d_6$ )  $\delta$  (ppm): 9.49 (s, 1H), 8.72 (d,  $J$ = 2.2 Hz, 1H), 8.07 (d,  $J$ = 9.0 Hz, 1H), 7.43 (s, 1H), 7.33 (d,  $J$ = 5.1 Hz, 1H), 7.26 (d,  $J$ = 8.4 Hz, 1H), 7.22 (d,  $J$ = 9.5 Hz, 1H), 7.04 to 7.02 (m, 1H), 6.89 (d,  $J$ = 9.2 Hz, 1H), 6.78 (d,  $J$ = 8.2 Hz, 1H), 5.13 (s, 2H), 3.62 (s, 4H), 2.44 to 2.38 (m, 4H), 2.22 (s, 3H).

Table 3: Characterization of compounds prepared according to Scheme 3

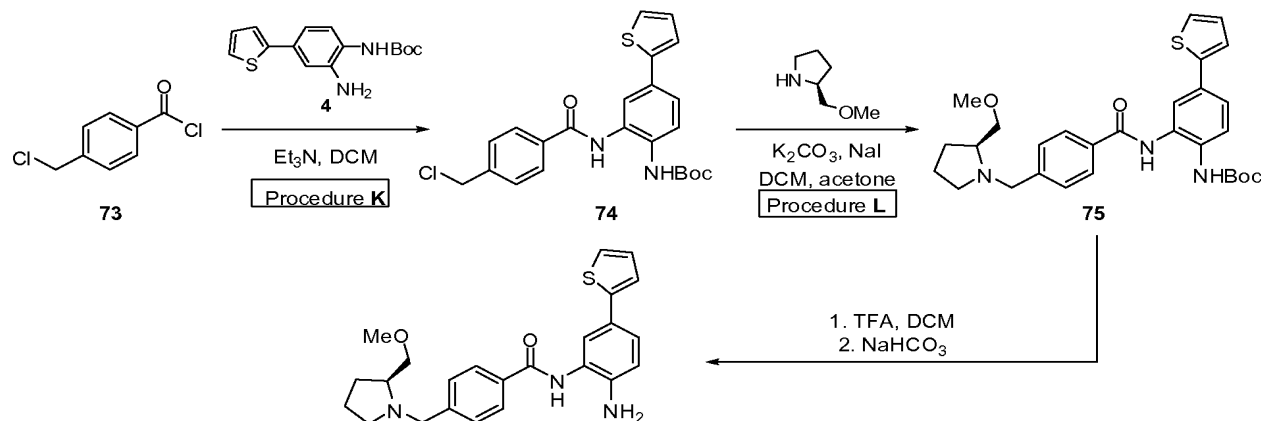


Cpd	Ex	R	Name	Characterization
<b>50</b>	<b>3c</b>		(R)- <i>N</i> -(2-amino-5-(thiophen-2-yl)phenyl)-6-(3-(dimethylamino)pyrrolidin-1-yl)nicotinamide	$^1\text{H}$ NMR (DMSO- $d_6$ ) $\delta$ (ppm): 9.47 (s, 1H), 8.72 (d, $J$ = 2.3 Hz, 1H), 8.05 (dd, $J$ = 9.0, 2.3 Hz, 1H), 7.44 (d, $J$ = 2.2 Hz, 1H), 7.34 (dd, $J$ = 5.1, 1.2 Hz, 1H), 7.26 (dd, $J$ = 8.4, 2.2 Hz, 1H), 7.23 (dd, $J$ = 3.5, 1.2 Hz, 1H), 7.03 (dd, $J$ = 5.1, 3.5 Hz, 1H), 6.78 (d, $J$ = 8.4 Hz, 1H), 6.52 (d, $J$ = 9.2 Hz, 1H), 5.11 (s, 2H), 3.37 to 3.35 (m, 1H), 3.19 to 3.12 (m, 2H), 2.80 to 2.74 (m, 2H), 2.20 (s, 6H), 2.18 to 2.12 (m, 1H), 1.85 to 1.78 (m, 1H). LRMS: 407.18 (calc) 408.2 (obs).
<b>51</b>	<b>3d</b>		<i>N</i> -(2-amino-5-(thiophen-2-yl)phenyl)-6-(4-morpholinopiperidin-1-yl)nicotinamide	$^1\text{H}$ NMR (DMSO- $d_6$ ) $\delta$ (ppm): 8.75 (d, $J$ =2.3 Hz, 1H), 8.09 (dd, $J_1$ =9.0 Hz, $J_2$ =2.3 Hz, 1H), 2.99 (d, $J$ =2.2 Hz, 1H), 7.34 (dd, $J_1$ =8.4 Hz, $J_2$ =2.2 Hz, 1), 7.21 (ddd, $J_1$ =9.6 Hz, $J_2$ =5.1 Hz, $J_3$ =1.0 Hz, 2H), 7.01 (dd, $J_1$ =5.1 Hz, $J_2$ =3.7 Hz, 1H), 6.88 (dd, $J_1$ =8.2 Hz, $J_2$ =5.1 Hz, 2H), 4.55 (d, $J$ =14 Hz, 2H), 3.73 (t, $J$ =4.5 Hz, 4H), 2.96 (td, $J_1$ =13 Hz, $J_2$ =2.2 Hz, 2H), 2.69 (bs, 4H), 2.62 (m, 1H), 2.04 (d, $J$ =12 Hz, 2H), 1.49 (qd, $J_1$ =12 Hz, $J_2$ =3.7 Hz, 2H). LRMS: 463.2 (calc) 464.1 (obs)

## Example 6a

**(S)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-((2-(methoxymethyl)pyrrolidin-1-yl)methyl)benzamide (76)**

## Scheme 6



76: example 6a

Step 1: *tert*-Butyl 2-(4-(chloromethyl)benzamido)-4-(thiophen-2-yl)phenylcarbamate (74)

[0706] To a suspension of amine **4** (0.45 g, 1.55 mmol) in DCM (6.84 mL), cooled to -20 °C, was added triethylamine (0.65 mL, 4.65 mmol) followed by a solution of 4-(chloromethyl)benzoyl chloride **73** (0.322 g, 1.71 mmol) in DCM (2.28 mL) via canula. The cold bath was then removed and the reaction mixture was stirred at room temperature for 1 h, washed with saturated NH<sub>4</sub>Cl, saturated NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The crude material was recrystallized from 30% AcOEt in hexane to give title compound **74** (0.431 g, 63 % yield).

[0707] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.92 (s, 1H), 8.73 (s, 1H), 7.97 (s, J = 8.2 Hz, 2H), 7.80 (d, J = 1.9 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.51 (dd, J = 4.9, 1.0 Hz, 1H), 7.50 (dd, J = 5.3, 2.3 Hz, 1H), 7.44 (dd, J = 3.7, 1.3 Hz, 1H), 7.11 (d, J = 5.1, 3.5 Hz, 1H), 4.84 (s, 2H), 1.44 (s, 9H).

Step 2: (S)-*tert*-Butyl 2-(4-((2-(methoxymethyl)pyrrolidin-1-yl)methyl)benzamido)-4-(thiophen-2-yl)phenylcarbamate (75)

[0708] To a solution of chloride **74** (0.30 g, 0.68 mmol) in DCM (7 mL) was added (S)-2-(methoxymethyl)pyrrolidine (86 mg, 0.75 mmol), K<sub>2</sub>CO<sub>3</sub> (0.31 g, 2.24 mmol) and NaI (12 mg, 0.075 mmol). Acetone (3 mL) was added and the reaction mixture was heated to reflux for 3

days then concentrated. The residue was taken up in AcOEt, washed with H<sub>2</sub>O, brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give title compound **75** (0.323 g, 91% yield).

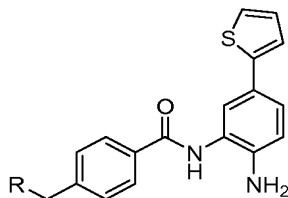
**[0709]** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.87 (s, 1H), 8.72 (s, 1H), 7.91 (d, J= 8.4 Hz, 2H), 7.80 (d, J= 2.2 Hz, 1H), 7.59 (d, J= 8.6 Hz, 1H), 7.51 (dd, J= 4.9, 1.0 Hz, 1H), 7.49 (dd, J= 8.4, 2.3 Hz, 1H), 7.45 (d, J= 8.6 Hz, 2H), 7.44 (dd, J= 3.7, 1.0 Hz, 1H), 7.11 (dd, J= 12.5 Hz, 1H), 3.39 (q, J= 5.7 Hz, 1H), 2.79 to 2.75 (m, 1H), 2.73 to 2.67 (m, 1H), 2.15 (q, J= 7.6 Hz, 1H), 1.86 (dq, J= 11.9, 7.8 Hz, 1H), 1.66 to 1.58 (m, 1H), 1.54 to 1.46 (m, 1H), 1.44 (s, 9H).

Step 3: (S)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-((2-(methoxymethyl)pyrrolidin-1-yl)methyl)benzamide (76)


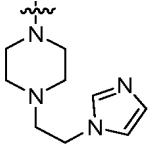
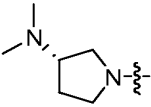
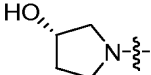
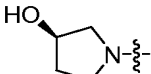
**[0710]** Following the same procedure as described in Example 1a, step 7 (scheme 1), but substituting compound 8 for 75, the title compound 76 was obtained (82% yield).

**[0711]** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.69 (s, 1H), 7.93 (d, J=8.2 Hz, 2H), 7.45 (d, J=1.8 Hz, 1H), 7.41 (d, J=8.2 Hz, 2H), 7.33 (dd, J=5.1, 1.0 Hz, 1H), 7.28 (dd, 8.2, 2.2 Hz, 1H), 7.23 (dd, J=3.5, 1.0 Hz, 1H), 7.03 (dd, J=4.9, 3.5 Hz, 1H), 3.43-3.37 (m, 2H), 3.27-3.21 (m, 1H), 3.24 (s, 3H), 2.79-2.74 (m, 1H), 2.71-2.66 (m, 1H), 1.65-1.59 (m, 1H), 1.58-1.47 (m, 1H).

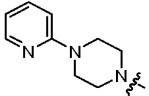
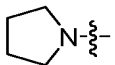
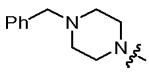
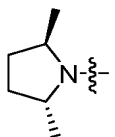
Table 6: Characterization of compounds prepared according to Scheme 6



Cpd	Ex	R	Name	Characterization
77	6b		N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-morpholinopiperidin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.83 (s, 1H), 8.08 (d, J=7.4 Hz, 2H), 7.63-7.60 (m, 2H), 7.44 (d, J=2.0 Hz, 1H), 7.35 (dd, J=5.1, 1.0 Hz, 1H), 7.31 (dd, J=8.2, 2.2 Hz, 1H), 7.23 (dd, J=3.5, 1.0 Hz, 1H), 7.04 (dd, J=5.1, 3.5 Hz, 1H), 6.81 (d, J=8.4 Hz, 1H), 4.43-4.32 (m, 2H), 4.05-3.82 (m, 2H), 3.76-3.60 (m, 2H), 3.60-3.27 (m, 5H), 3.06-2.87 (m, 4H), 2.28-2.19 (m, 2H), 1.92-1.78 (m, 2H). LRMS: 476.6 (calc) 477.1 (obs)
78	6c		N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.70 (s, 1H), 7.94 (d, J=8.0 Hz, 2H), 7.44 (d, J=2.0 Hz, 1H), 7.41 (d, J=8.2 Hz, 2H), 7.34 (dd, J=5.1, 1.0 Hz, 1H), 7.28 (dd, J=8.4, 2.3 Hz, 1H), 7.22 (dd, J=3.5, 1.2 Hz, 1H), 7.03 (dd, J=5.1, 3.5 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 3.52 (s, 2H), 2.52-2.31 (m, 4H), 2.22-2.17 (m, 4H), 2.07 (s, 3H). LRMS: 406.6 (calc) 407.1 (obs)

Cpd	Ex	R	Name	Characterization
79	6d		N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((diethylamino)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.69 (s, 1H), 7.93 (d, J=7.4 Hz, 2H), 7.45 (d, J=2.2 Hz, 1H), 7.43 (d, J=8.6 Hz, 2H), 7.34 (dd, J=5.1, 1.2 Hz, 1H), 7.28 (dd, J=8.2, 2.2 Hz, 1H), 7.22 (dd, J=3.7, 1.2 Hz, 1H), 7.03 (dd, J=5.1, 3.5 Hz, 1H), 6.79 (d, J=8.2 Hz, 1H), 5.14 (s, 2H), 3.58 (s, 2H), 2.45 (q, J=7.2 Hz, 4H), 0.97 (t, J=6.7 Hz, 6H). LRMS: 379.5 (calc) 380.1 (obs).
80	6e		4-((4-(2-(1H-imidazol-1-yl)ethyl)piperazin-1-yl)methyl)-N-(2-amino-5-(thiophen-2-yl)phenyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.70 (s, 1H), 7.95 (d, J=8.0 Hz, 2H), 7.65 (s, 1H), 7.45 (d, J=2.1 Hz, 1H), 7.41 (d, J=8.2 Hz, 2H), 7.34 (dd, J=5.1, 4.1 Hz, 1H), 7.28 (dd, J=8.4, 2.2 Hz, 1H), 7.22 (dd, J=3.5, 1.2 Hz, 1H), 7.17 (s, 1H), 7.03 (dd, J=5.1, 3.5 Hz, 1H), 6.86 (s, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 4.04 (t, J=6.5 Hz, 2H), 3.54 (s, 2H), 2.59 (t, J=6.3 Hz, 2H), 2.47-2.38 (m, 8H). LRMS: 486.6 (calc) 487.1 (obs)
81	6f		(S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.70 (s, 1H), 7.94 (d, J=8.2 Hz, 2H), 7.45 (d, J=2.2 Hz, 1H), 7.41 (d, J=8.4 Hz, 2H), 7.34 (dd, J=5.1, 1.0 Hz, 1H), 7.28 (dd, J=8.4, 2.2 Hz, 1H), 7.22 (dd, J=3.5, 1.0 Hz, 1H), 7.03 (dd, J=5.1, 3.7 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 3.66 (d, J=13.4 Hz, 1H), 3.55 (d, J=13.5 Hz, 1H), 2.72-2.60 (m, 2H), 2.60-2.54 (m, 1H), 2.48-2.41 (m, 1H), 2.28-2.22 (m, 1H), 1.88-1.79 (m, 1H), 1.63-1.55 (m, 1H). LRMS: 420.6 (calc) 421.1 (obs)
82	6g		(S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-hydroxypyrrolidin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.71 (s, 1H), 7.94 (d, J=8.0 Hz, 2H), 7.45 (d, J=1.8 Hz, 1H), 7.42 (d, J=8.0 Hz, 2H), 7.34 (dd, J=5.1, 1.2 Hz, 1H), 7.28 (dd, J=8.4, 2.2 Hz, 1H), 7.23 (dd, J=3.5, 1.0 Hz, 1H), 7.03 (dd, J=5.1, 1.6 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 4.74-4.68 (m, 1H), 4.23-4.17 (m, 1H), 3.69-3.57 (m, 2H), 2.72-2.36 (m, 1H), 2.62-2.53 (m, 1H), 2.43-2.36 (m, 1H), 2.34-2.29 (m, 1H), 1.99 (sext, J=6.8 Hz, 1H), 1.58-1.50 (m, 1H). LRMS: 393.5 (calc) 394.10 (obs)
83	6h		(R)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-hydroxypyrrolidin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.71 (s, 1H), 7.94 (d, J=8.2 Hz, 2H), 7.45 (d, J=2.2 Hz, 1H), 7.43 (d, J=8.2 Hz, 2H), 7.34 (dd, J=5.1, 1.2 Hz, 1H), 7.28 (d, J=8.2, 2.2 Hz, 1H), 7.23 (dd, J=3.5, 1.0 Hz, 1H), 7.03 (dd, J=5.1, 3.5 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 4.76-4.69 (m, 1H), 4.24-4.16 (m, 1H), 3.70-3.57 (m, 2H), 2.72-2.63 (m, 1H), 2.63-2.53 (m, 1H), 2.46-2.36 (m, 1H), 2.35-2.28 (m, 1H), 1.99 (sext, J=7.2 Hz, 1H), 1.59-1.52 (m, 1H). LRMS: 393.5 (calc) 394.1 (obs)

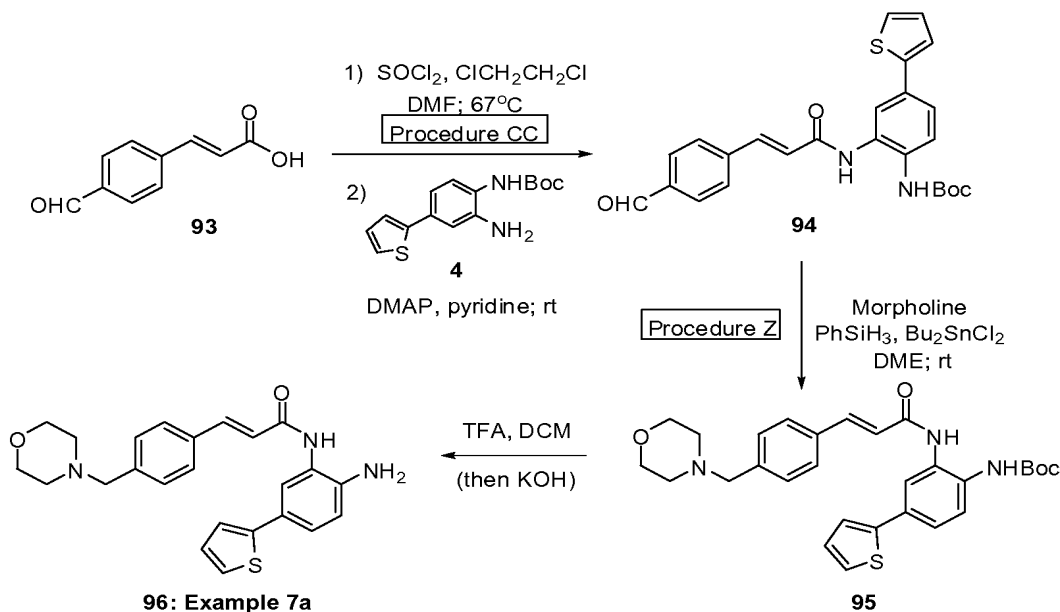
Cpd	Ex	R	Name	Characterization
84	6i		(R)-4-((3-acetamidopyrrolidin-1-yl)methyl)-N-(2-amino-5-(thiophen-2-yl)phenyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.70 (s, 1H), 8.00 (d, J=6.9 Hz, 1H), 7.94 (d, J=8.0 Hz, 2H), 7.45 (d, J=2.2 Hz, 1H), 7.43 (d, J=8.2 Hz, 2H), 7.34 (dd, J=5.1, 1.2 Hz, 1H), 7.28 (d, J=8.2, 2.2 Hz, 1H), 7.23 (dd, J=3.7, 1.2 Hz, 1H), 7.03 (dd, J=5.1, 3.5 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 4.16-4.07 (m, 1H), 3.64 (d, J=13.3 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 2.67-2.58 (m, 2H), 2.41-2.35 (m, 1H), 2.28 (dd, J=9.4, 4.3 Hz, 1H), 2.11-2.03 (m, 1H), 1.75 (s, 3H), 1.60-1.50 (m, 1H). LRMS: 434.6 (calc) 435.1 (obs)
85	6j		N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-(pyridin-4-yl)piperazin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.71 (s, 1H), 8.13 (d, J=6.7 Hz, 2H), 7.97 (d, J=8.0 Hz, 2H), 7.46 (d, J=8.2 Hz, 2H), 7.45 (s, 1H), 7.34 (dd, J=5.1, 1.2 Hz, 1H), 7.28 (dd, J=8.4, 2.2 Hz, 1H), 7.23 (dd, J=3.5, 1.2 Hz, 1H), 7.03 (dd, J=5.1, 1.6 Hz, 1H), 6.79 (d, J=8.4 Hz, 2H), 6.79 (d, J=4.6 Hz, 1H), 5.14 (s, 2H), 3.60 (s, 2H), 3.36-3.28 (m, 8H). LRMS: 469.6 (calc) 470.1 (obs)
86	6k		(S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((2-(pyrrolidin-1-yl)methyl)pyrrolidin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.74 (s, 1H), 7.97 (d, J=8.0 Hz, 2H), 7.47 (d, J=8.4 Hz, 2H), 7.45 (d, J=2.0 Hz, 1H), 7.34 (dd, J=5.1, 1.2 Hz, 1H), 7.29 (dd, J=8.2, 2.2 Hz, 1H), 7.03 (dd, J=5.1, 3.5 Hz, 1H), 6.80 (d, J=8.4 Hz, 1H), 5.15 (s, 2H), 4.13 (d, J=13.5 Hz, 1H), 4.47 (d, J=13.9 Hz, 1H), 3.33-3.20 (m, 5H), 3.16-3.12 (m, 1H), 3.08-2.96 (m, 1H), 2.84-2.80 (m, 1H), 2.33-2.27 (m, 1H), 2.12-2.02 (m, 1H), 1.96-1.88 (m, 4H), 1.78-1.63 (m, 3H). LRMS: 460.6 (calc) 461.2 (obs).
87	6l		(S)-4-((3-acetamidopyrrolidin-1-yl)methyl)-N-(2-amino-5-(thiophen-2-yl)phenyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.69 (s, 1H), 7.99 (d, J=6.3 Hz, 1H), 7.94 (d, J=8.2 Hz, 2H), 7.45 (d, J=2.2 Hz, 1H), 7.43 (d, J=8.4 Hz, 2H), 7.34 (dd, J=5.1, 1.2 Hz, 1H), 7.28 (dd, J=8.2, 2.2 Hz, 1H), 7.22 (dd, J=3.5, 1.2 Hz, 1H), 7.03 (dd, J=5.1, 3.5 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 4.17-4.07 (m, 2H), 3.64 (d, J=13.3 Hz, 1H), 3.60 (d, J=13.7 Hz, 1H), 2.66-2.57 (m, 2H), 2.39 (q, J=8.6 Hz, 1H), 2.28 (dd, J=9.2, 4.1 Hz, 1H), 2.33-2.03 (m, 1H), 1.75 (s, 3H), 1.55 (sext, J=6.8 Hz, 1H). LRMS: 434.6 (calc) 435.1 (obs).
88	6m		N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((methyl(pyridin-3-yl)methyl)amino)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.70 (s, 1H), 8.53 (s, 1H), 8.47 (dd, J=4.7, 1.8 Hz, 1H), 7.97 (d, J=8.0 Hz, 2H), 7.76 (d, J=7.8, 4.7 Hz, 1H), 7.47 (d, J=8.0 Hz, 2H), 7.45 (d, J=2.0 Hz, 1H), 7.37 (dd, J=7.8, 4.7 Hz, 1H), 7.34 (dd, J=4.9, 1.0 Hz, 1H), 7.28 (dd, J=8.2, 2.2 Hz, 1H), 7.22 (dd, J=3.5, 1.0 Hz, 1H), 7.03 (dd, J=5.3, 3.7 Hz, 1H), 6.79 (d, J=8.2 Hz, 1H), 5.13 (s, 2H), 3.59 (s, 2H), 3.55 (s, 2H), 2.09 (s, 3H). LRMS: 428.6 (calc) 429.1 (obs).

Cpd	Ex	R	Name	Characterization
89	6n		N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-(pyridin-2-yl)piperazin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.71 (s, 1H), 8.08 (dd, J=4.9, 1.2 Hz, 1H), 7.97 (d, J=8.0 Hz, 1H), 7.51 (dd, J=7.2, 2.2 Hz, 1H), 7.49 (dd, J=6.9, 1.8 Hz, 1H), 7.47 (d, J=8.2 Hz, 2H), 7.34 (dd, J=5.1, 1.2 Hz, 1H), 7.28 (d, J=8.1, 2.3 Hz, 1H), 7.23 (dd, J=3.7, 1.2 Hz, 1H), 7.03 (dd, J=5.1, 3.5 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 6.61 (dd, J=6.5, 4.9 Hz, 1H), 5.15 (s, 2H), 3.59 (s, 2H), 3.49-3.46 (m, 4H), 2.48-2.45 (m, 4H). LRMS: 469.6 (calc) 470.2 (obs).
90	6o		N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(pyrrolidin-1-ylmethyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.71 (s, 1H), 7.95 (d, J=7.0 Hz, 2H), 7.45 (s, 3H), 7.34 (dd, J=5.1, 1.0 Hz, 1H), 7.28 (dd, J=8.4, 2.2 Hz, 1H), 7.23 (dd, J=9.3, 0.78 Hz, 1H), 7.03 (dd, J=5.1, 3.7 Hz, 1H), 6.80 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 3.65 (bs, 2H), 2.47 (bs, 4H), 1.72 (bs, 4H). LRMS: 377.5 (calc) 378.1 (obs).
91	6p		N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((4-benzylpiperazin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.70 (s, 1H), 7.94 (d, J=8.2 Hz, 2H), 7.45 (s, 1H), 7.41 (d, J=8.0 Hz, 2H), 7.34 (d, J=5.1 Hz, 1H), 7.32-7.26 (m, 5H), 7.23-7.20 (m, 2H), 7.03 (dd, J=5.1, 3.7 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 3.53 (s, 2H), 3.44 (s, 2H), 2.48-2.37 (m, 8H). LRMS: 482.7 (calc) 483.1 (obs).
92	6q		N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(((2R,5R)-2,5-dimethylpyrrolidin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.18 (s, 1H), 8.02 (d, J=8.0 Hz, 2H), 7.66 (d, J=2.5 Hz, 1H), 7.59-7.51 (m, 2H), 7.34 (dd, J=8.2, 2.2 Hz, 1H), 7.29 (dd, J=5.3, 1.2 Hz, 1H), 7.25 (dd, J=3.5, 1.2 Hz, 1H), 7.04 (dd, J=5.1, 3.5 Hz, 1H), 6.92 (d, J=8.4 Hz, 1H), 4.87 (bs, 2H), 3.93 (d, J=12.5 Hz, 1H), 3.67 (d, J=12.5 Hz, 1H), 3.05 (bs, 2H), 2.05 (bs, 2H), 1.38 (bs, 2H), 0.99 (bs, 6H). LRMS: 405.6 (calc) 406.1 (obs).

### Example 7a

**(E)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-3-(4-(morpholinomethyl)phenyl)acrylamide (96)**

## Scheme 7

Step 1: (E)-tert-Butyl 2-(3-(4-formylphenyl)acrylamido)-4-(thiophen-2-yl)phenyl-carbamate (94)

[0712] A suspension of (E)-3-(4-formylphenyl)acrylic acid **93** (1.046g, 5.94 mmol) in 1,2-dichloroethane (30 mL) was treated with neat thionyl chloride ( $\text{SOCl}_2$ ) (0.9 mL, 12.3 mmol) and stirred at 67 °C then dimethyl formamide (0.3 mL) was slowly added; and the reaction mixture was allowed to stir at 67 °C for 30 min, cooled to room temperature, concentrated, diluted with dry benzene (40 mL) and concentrated again. The yellow residue was stored under vacuum for 3 h then suspended in pyridine (25 mL) and treated with amine **4** (1.113g, 3.83 mmol) and 4-dimethylamino pyridine (DMAP) (156 mg). The suspension was stirred at room temperature for 3 days, diluted with  $\text{H}_2\text{O}$  (10 mL) then stirred for additional 5 h. The solution was diluted with DCM, washed with 5%  $\text{KHSO}_4$ , saturated  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$ , filtered and concentrated to provide title compound **94** (0.415g, 24% yield) after purification by flash chromatography (eluent: 30% to 50% AcOEt in hexanes). LRMS: 448.2 (calc) 471.0 ( $\text{M}+\text{Na}$ , obs)

Step 2: (E)-tert-Butyl 2-(3-(4-(morpholinomethyl)phenyl)acrylamido)-4-(thiophen-2-yl)phenylcarbamate (95)

[0713] A mixture of aldehyde **94** (0.205 g, 0.458 mmol) and dibutyltin dichloride (87 mg, 0.28 mmol) was suspended in ethyleneglycol dimethylether (1.5 mL) and stirred for 15 minutes then treated with phenyl silane (0.15 mL, 1.18 mmol) and the yellow suspension was stirred at



room temperature for 15 h. The reaction mixture was quenched with MeOH, stirred for 3 h, concentrated then purified by column chromatography (eluent: 5% isopropanol in DCM) followed by trituration with a diethyl ether and pentane mixture to provide title compound **95** (0.124 g, 100% yield). LRMS: 519.2 (calc) 520.1 (obs)

Step 3: (E)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-3-(4-(morpholinomethyl)phenyl)-acrylamide (**96**)

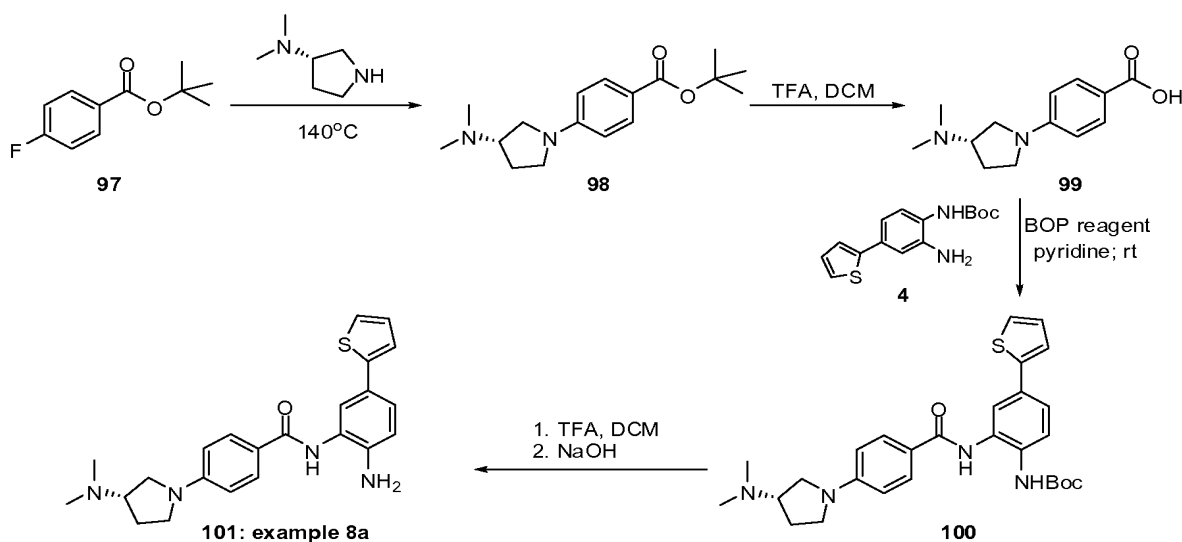
[0714] Following the same procedure as described in Example 1, step 7 (scheme 1), but substituting compound **8** for compound **95**, the title compound **96** was obtained (0.161g, 67% yield).

[0715]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 9.46 (s, 1H), 7.70 (d,  $J$  = 2.2 Hz, 1H), 7.60 to 7.55 (m, 3H), 7.40 to 7.35 (m, 3H), 7.26 to 7.22 (m, 2H), 7.05 (dd,  $J$  = 5.1, 3.5 Hz, 1H), 6.89 (d,  $J$  = 15.7 Hz, 1H), 6.78 (d,  $J$  = 8.4 Hz, 1H), 5.22 (s, 2H), 3.58 (t,  $J$  = 4.5 Hz, 4H), 3.49 (s, 2H), 2.36 (m, 4H). LRMS: 419.2 (calc) 420.0 (obs)

### Example 8a

**(S)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)benzamide (**101**)**

#### Scheme 8



Step 1: (S)-tert-Butyl 4-(3-(dimethylamino)pyrrolidin-1-yl)benzoate (**98**)

[0716] A mixture of fluoride **97** (2.196 g, 11.2 mmol) and (S)-N,N-dimethylpyrrolidin-3-amine (1.369 g, 11.99 mmol) was stirred at 140 °C under nitrogen atmosphere for 3 h then diluted with DCM, washed with saturated  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$ , filtered and

concentrated. The crude compound was purified by flash chromatography (eluent: 50% AcOEt in DCM then 50% isopropanol in DCM with 0.1% triethylamine) to give title compound **98** (1.36 g, 42% yield).

[0717]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 7.67 (d,  $J$ = 9.0 Hz, 2H), 6.52 (d,  $J$ = 9.0 Hz, 2H), 3.50 (dd,  $J$ = 9.8, 7.2 Hz, 1H), 3.45 to 3.39 (m, 1H), 3.30 to 3.24 (m, 1H), 3.06 (t,  $J$ = 8.2 Hz, 1H), 2.83 to 2.75 (m, 1H), 2.20 (s, 6H), 2.17 to 2.14 (m, 1H), 1.86 to 1.76 (m, 1H), 1.51 (s, 9H).

Step 2: (S)-4-(3-(Dimethylamino)pyrrolidin-1-yl)benzoic acid (**99**)

[0718] A solution of *tert*-butyl ester **98** (0.595 g, 2.05 mmol) in 1:1 trifluoroacetic acid: DCM (6 mL) was stirred at room temperature for 3 h then concentrated to give title compound **99** (used as is in the next reaction). LRMS: 234.14 (calc) 235.1 (obs)

Step 3: (S)-*tert*-Butyl 2-(4-(3-(dimethylamino)pyrrolidin-1-yl)benzamido)-4-(thiophen-2-yl)phenylcarbamate (**100**)

[0719] Following the same procedure as described in Example **1a**, step 6 (scheme 1) and using compound **4** but substituting compound **7** for compound **99**, the title compound **100** was obtained (0.407 g, 68% yield) [after flash chromatography (eluent: 10% isopropanol in DCM with 0.1% triethylamine)].

[0720]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 9.63 (s, 1H), 8.67 (s, 1H), 7.82 (d,  $J$ = 8.8 Hz, 2H), 7.78 (d,  $J$ = 2.0 Hz, 1H), 7.54 (d,  $J$ = 8.4 Hz, 1H), 7.50 (dd,  $J$ = 8.4 Hz, 1H), 7.46 (d,  $J$ = 2.2 Hz, 1H), 7.45 to 7.42 (m, 1H), 7.12 to 7.09 (m, 1H), 6.60 (d,  $J$ = 9.0 Hz, 2H), 3.56 to 3.52 (m, 1H), 3.46 (t,  $J$ = 8.8 Hz, 1H), 3.92 to 3.27 (m, 1H), 3.16 to 3.04 (m, 1H), 2.83 to 2.76 (m, 1H), 2.21 (s, 6H), 2.16 (m, 1H), 1.87 to 1.77 (m, 1H), 1.46 (s, 9H).

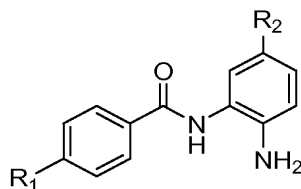
Step 4: (S)-*N*-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)benzamide (**101**)

[0721] Following the same procedure as described in Example **1a**, step 7 (scheme 1), but substituting compound **8** for compound **100**, the title compound **101** was obtained (0.229 g, 70% yield). [Crude product was triturated with diethyl ether while the mother liquor was concentrated and purified by flash chromatography (eluent: 5% to 10% isopropanol in DCM)].

[0722]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 9.41 (s, 1H), 7.86 (d,  $J$ = 8.6 Hz, 2H), 7.44 (d,  $J$ = 2.2 Hz, 1H), 7.34 (dd,  $J$ = 5.1, 0.98 Hz, 1H), 7.25 (dd,  $J$ = 8.2, 2.2 Hz, 1H), 7.23 (dd,  $J$ = 3.5, 0.98 Hz, 1H), 7.04 to 7.02 (m, 1H), 6.79 (d,  $J$ = 8.4 Hz, 1H), 6.58 (d,  $J$ = 8.8 Hz, 2H), 5.07 (s, 2H), 3.56 to 3.51 (m, 1H), 3.46 (t,  $J$ = 8.4 Hz, 1H), 3.32 to 3.27 (m, 1H), 3.09 (t,  $J$ = 8.2 Hz, 1H), 2.84 to 2.76

(m, 1H), 2.22 (s, 6H), 2.19 to 2.16 (m, 1H), 1.88 to 1.78 (m, 1H). LRMS: 406.1 (calc), 407.1 (obs).

Table 7: Characterization of compounds prepared according to Scheme 8



Cpd	Ex	R <sub>1</sub>	R <sub>2</sub>	Name	Characterization
102	8b			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-isopropylpiperazin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.50 (s, 1H), 7.89 (d, J= 9.0 Hz, 2H), 7.46 (d, J= 2.2 Hz, 1H), 7.36 (dd, J= 5.1, 1.2 Hz, 1H), 7.28 (dd, J= 8.2, 2.2 Hz, 1H), 7.24 (dd, J= 3.5, 0.98 Hz, 1H), 7.05 (dd, J= 5.1, 3.5 Hz, 1H), 7.00 (d, J= 9.0 Hz, 2H), 6.80 (d, J= 8.2 Hz, 1H), 5.10 (s, 2H), 3.28 to 3.26 (m, 4H), 2.70 (m, 1H), 2.58 (m, 4H), 1.01 (d, J= 6.5 Hz, 6H). LRMS: 420.2 (calc) 421.2 (obs).
103	8c			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-cyclopentylpiperazin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.51 (s, 1H), 7.89 (d, J= 8.4 Hz, 2H), 7.45 (d, J= 2.3 Hz, 1H), 7.36 (dd, J= 5.1, 0.98 Hz, 1H), 7.28 (dd, J= 8.2, 2.2 Hz, 1H), 7.24 (dd, J= 3.5, 1.2 Hz, 1H), 7.05 (dd, J= 5.1, 3.5 Hz, 1H), 7.01 (m, 2H), 6.81 (d, J= 8.4 Hz, 1H), 5.10 (s, 2H), 3.31 to 3.28 (m, 4H), 2.55 to 2.52 (m, 4H), 1.82 (m, 2H), 1.64 (m, 3H), 1.53 (m, 2H), 1.37 to 1.34 (m, 2H). LRMS: 446.2 (calc) 447.2 (obs).
104	8d			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-morpholinopiperidin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.49 (s, 1H), 7.87 (d, J= 9.0 Hz, 2H), 7.45 (d, J= 2.2 Hz, 1H), 7.36 (dd, J= 5.1, 1.2 Hz, 1H), 7.28 (dd, J= 8.4, 2.3 Hz, 1H), 7.24 (dd, J= 3.5, 1.2 Hz, 1H), 7.05 (dd, J= 5.1, 3.7 Hz, 1H), 7.00 (d, J= 9.2 Hz, 2H), 6.80 (d, J= 8.4 Hz, 1H), 5.09 (s, 2H), 3.92 (d, J= 13.7 Hz, 2H), 3.57 (t, J= 4.3 Hz, 4H), 2.81 (t, J= 11.3 Hz, 2H), 2.48 to 2.46 (m, 4H), 2.36 to 2.32 (m, 1H), 1.87 to 1.84 (m, 2H), 1.49 to 1.41 (m, 2H). LRMS: 462.2 (calc) 463.2 (obs).

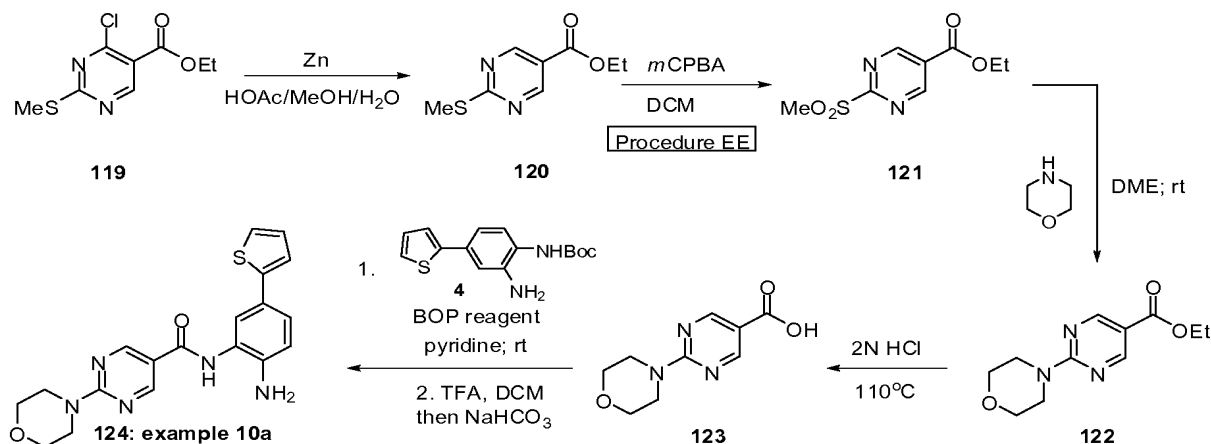
Cpd	Ex	R <sub>1</sub>	R <sub>2</sub>	Name	Characterization
105	8e			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-(pyrrolidin-1-yl)piperidin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.49 (s, 1H), 7.88 (d, J= 9.0 Hz, 2H), 7.45 (d, J= 2.2 Hz, 1H), 7.36 (dd, J= 5.1, 1.2 Hz, 1H), 7.28 (dd, J= 8.4, 2.3 Hz, 1H), 7.25 (dd, J= 3.7, 1.2 Hz, 1H), 7.05 (dd, J= 5.1, 3.5 Hz, 1H), 7.00 (d, J= 9.2 Hz, 2H), 6.80 (d, J= 8.4 Hz, 1H), 5.09 (s, 2H), 3.81 (m, 2H), 3.31 to 3.28 (m, 2H), 2.87 (t, J= 11.0 Hz, 2H), 2.67 to 2.66 (m, 1H), 2.46 to 2.45 (m, 1H), 2.33 to 2.32 (m, 1H), 1.91 (m, 2H), 1.69 (m, 4H), 1.49 to 1.47 (m, 2H). LRMS: 446.2 (calc) 447.2 (obs).
106	8f			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(2-(dimethylamino)ethylthio)benzamide	<sup>1</sup> H NMR (Acetone-d <sub>6</sub> ) δ (ppm): 9.33 (bs, 1H), 8.14 (d, J=8.4 Hz, 2H), 7.77 (d, J=2.3 Hz, 1H), 7.60 (d, J=8.4 Hz, 2H), 7.48 (dd, J=8.4, 2.2 Hz, 1H), 7.42 (dd, J=5.1, 1.2 Hz, 1H), 7.37 (dd, J=3.7, 1.2 Hz, 1H), 7.18 (dd, J=5.1, 3.5 Hz, 1H), 7.05 (d, J=8.4 Hz, 1H), 4.99 (bs, 2H), 3.41-3.37 (m, 2H), 2.87 (t, J=7.4 Hz, 2H), 2.50 (s, 6H). LRMS: 397.56 (calc) 398.1 (obs).
107	8g			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(2-(diethylamino)ethylthio)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.69 (s, 1H), 7.92 (d, J=8.4 Hz, 2H), 7.44 (d, J=2.0 Hz, 1H), 7.41 (d, J=8.6 Hz, 2H), 7.34 (dd, J=5.1, 1.2 Hz, 1H), 7.28 (dd, J=8.4, 2.3 Hz, 1H), 7.22 (d, J=1.2 Hz, 1H), 7.03 (dd, J=5.1, 3.7 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 3.12 (t, J=6.8 Hz, 2H), 2.68-2.62 (m, 2H), 2.48 (q, J=7.2 Hz, 4H), 0.94 (t, J=7.0 Hz, 6H). LRMS: 425.62 (calc) 426.1 (obs).
108	8h			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-(2-methoxyethyl)piperazin-1-yl)benzamide	<sup>1</sup> H NMR (Acetone-d <sub>6</sub> ) δ (ppm): 8.01 (d, J=9.0 Hz, 2H), 7.68 (d, J=2.3 Hz, 1H), 7.38 (dd, J=3.5, 1.2 Hz, 1H), 7.10-7.07 (m, 3H), 6.95 (d, J=8.2 Hz, 1H), 3.61 (t, J=5.7 Hz, 2H), 3.44-3.38 (m, 2H), 3.35 (s, 3H), 2.80-2.65 (m, 8H). LRMS: 436.58 (calc) 437.1 (obs).

Cpd	Ex	R <sub>1</sub>	R <sub>2</sub>	Name	Characterization
109	8i			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-(pyridin-4-yl)piperazin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.55, (s, 1H), 8.22 (d, J= 6.1 Hz, 2H), 7.93 (d, J= 9.0 Hz, 2H), 7.46 (d, J= 2.2 Hz, 1H), 7.36 (dd, J= 5.1, 1.2 Hz, 1H), 7.29 (dd, J= 8.2, 2.2 Hz, 1H), 7.25 (dd, J= 3.5, 1.2 Hz, 1H), 7.07 to 7.04 (m, 3H), 6.99 (d, J= 6.3 Hz, 2H), 6.81 (d, J= 8.4 Hz, 1H), 5.11 (s, 2H), 3.61 (t, J= 4.3 Hz, 4H), 3.49 to 3.46 (m, 4H). LRMS: 455.1 (calc) 456.0 (obs).
110	8j			N-(2-amino-5-(5-chlorothiophen-2-yl)phenyl)-4-(4-(pyridin-4-yl)piperazin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.53 (s, 1H), 8.20 (d, J= 6.3 Hz, 2H), 8.16 (s, 1H, from formic acid salt), 7.92 (d, J= 9.0 Hz, 2H), 7.40 (d, J= 2.2 Hz, 1H), 7.23 (dd, J= 8.4, 2.3 Hz, 1H), 7.11 (d, J= 3.9 Hz, 1H), 7.08 to 7.05 (m, 3H), 6.90 (d, J= 6.5 Hz, 2H), 6.80 (d, J= 8.4 Hz, 1H), 5.20 (s, 2H), 3.53 to 3.50 (m, 4H), 3.46 to 3.44 (m, 4H). LRMS: 490.2 (calc) 490.0 and 492.0 (obs).

### Example 10a

#### N-(2-Amino-5-(thiophen-2-yl)phenyl)-2-morpholinopyrimidine-5-carboxamide (124)

#### Scheme 10



#### Step 1: Ethyl 2-(methylthio)pyrimidine-5-carboxylate (120)

[0723] A solution of chloride **119** (1.51 g, 6.5 mmol) in acetic acid (5 mL) was treated with Zn(0) dust (0.969 g, 14.82 mmol). The suspension was stirred at room temperature for 24 h then diluted with DCM, filtered through Celite®, and concentrated. The residue was taken up in

DCM, washed with saturated NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered and concentrated to give title compound **120** (0.424 g, 33% yield).

[0724] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.00 (s, 1H), 4.36 to 4.29 (m, 2H), 3.33 (s, 1H), 2.58 (s, 3H), 1.35-1.32 (m, 3H).

Step 2: Ethyl 2-(methylsulfonyl)pyrimidine-5-carboxylate (**121**)

[0725] A solution of sulfide **120** (0.424 g, 2.14 mmol) in DCM (9 mL) was treated with a solution of 3-chloroperoxybenzoic acid (*m*CPBA) (2.0 g) in DCM (9 mL) then the reaction mixture was stirred at room temperature for 100 min, quenched with a solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> in H<sub>2</sub>O, diluted with DCM and washed with saturated NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered and concentrated to give compound **121** (0.374 g, 76% yield).

[0726] MS: 230.1 (calc) 230.9 (obs)

Step 3: Ethyl 2-morpholinopyrimidine-5-carboxylate (**122**)

[0727] A solution of sulfone **121** (0.184 g, 0.80 mmol) in ethyleneglycol dimethylether (5 mL) was treated with neat morpholine (0.3 mL, 3.4 mmol) and the mixture was stirred at room temperature for 48 h. The reaction mixture was then diluted with DCM and washed with saturated NaHCO<sub>3</sub> in brine, dried over MgSO<sub>4</sub>, filtered, concentrated and stored under vacuum to give intermediate **122** (0.205 g, >99% yield).

[0728] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 8.78 (s, 2H), 4.26 (q, J= 7.0 Hz, 2H), 3.83 (t, J= 4.7 Hz, 4H), 3.66 (t, J= 5.1 Hz, 4H), 1.30 (t, J= 7.0 Hz, 3H).

Step 4: 2-Morpholinopyrimidine-5-carboxylic acid (**123**)

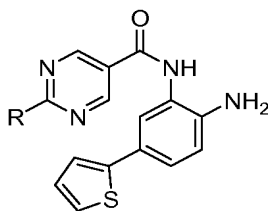
[0729] A solution of ester **122** (0.205 g, 0.86 mmol) in 2N HCl in H<sub>2</sub>O (10 mL) was stirred at 110 °C in a pressure vessel for 6 h, cooled to -78 °C and lyophilized for 2 days. The resulting amorphous solid was further dried using a mixture of dry acetonitrile (10 mL) and dry benzene (10 mL) followed by concentration (this was repeated 3 times) to give compound **123** (0.193 g, 92% yield). LRMS: 209.1 (calc) 210.0 (obs).

Steps 5 & 6: N-(2-Amino-5-(thiophen-2-yl)phenyl)-2-morpholinopyrimidine-5-carboxamide (**124**)

[0730] Following the same procedures as described in Example **1a**, steps 6 and 7 (scheme 1), but substituting compound **7** for compound **123**, the title compound **124** was obtained (Step 5: 66% yield, Step 6: 58% yield).

[0731]  $^1\text{H}$  NMR: (DMSO- $d_6$ )  $\delta$  (ppm): 9.60 (s, 1H), 8.94 (s, 2H), 7.45 (d,  $J$ = 2.2 Hz, 1H), 7.35 (dd,  $J$ = 5.1, 0.98 Hz, 1H), 7.29 (dd,  $J$ = 8.4, 2.2 Hz, 1H), 7.24 (dd,  $J$ = 3.5, 0.98 Hz, 1H), 7.05 (dd,  $J$ = 4.9, 3.5 Hz, 1H), 6.79 (d,  $J$ = 8.4 Hz, 1H), 5.22 (s, 2H), 3.84 to 3.82 (m, 4H), 3.69 to 3.67 (m, 4H). LRMS: 381.1 (calc), 382.0 (obs).

Table 9: Characterization of compounds prepared according to Scheme 10

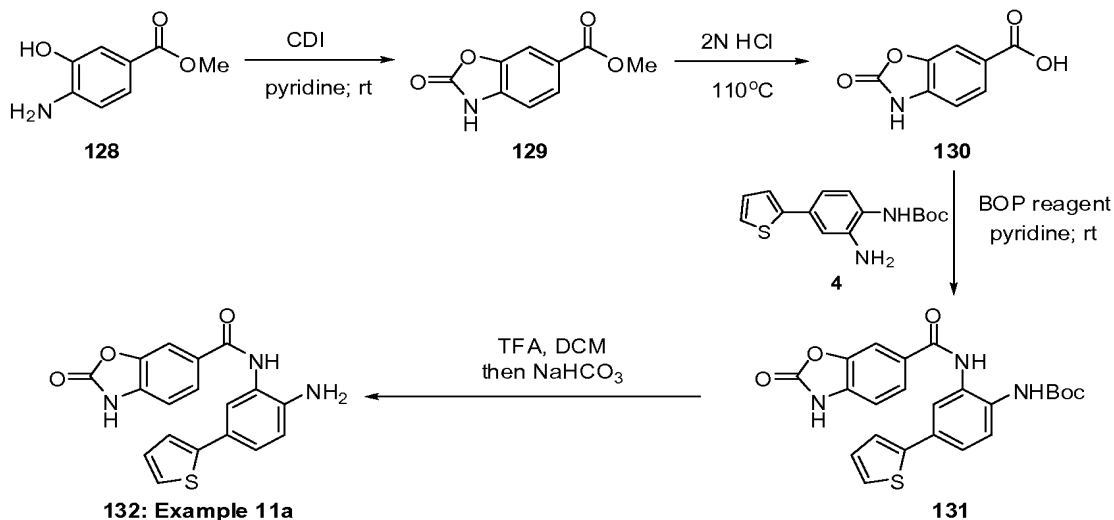


Cpd	Ex	R	Name	Characterization
125	10b		N-(2-amino-5-(thiophen-2-yl)phenyl)-2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxamide	$^1\text{H}$ NMR (DMSO- $d_6$ ) $\delta$ (ppm): 9.62 (s, 1H), 8.94 (s, 2H), 7.45 (d, $J$ = 2.2 Hz, 1H), 7.35 (dd, $J$ = 5.1, 1.2 Hz, 1H), 7.30 (dd, $J$ = 8.4, 2.3 Hz, 1H), 7.24 (dd, $J$ = 3.5, 0.98 Hz, 1H), 7.05 (dd, $J$ = 5.1, 3.5 Hz, 1H), 6.79 (d, $J$ = 8.4 Hz, 1H), 5.23 (s, 2H), 3.93 to 3.92 (m, 4H), 3.11 to 3.05 (m, 4H), 2.41 (s, 3H). LRMS: 394.1 (calc) 395.1 (obs).
126	10c		N-(2-amino-5-(thiophen-2-yl)phenyl)-2-(4-morpholinopiperidin-1-yl)pyrimidine-5-carboxamide	$^1\text{H}$ NMR (DMSO- $d_6$ ) $\delta$ (ppm): 9.56 (s, 1H), 8.90 (s, 2H), 7.44 (d, $J$ = 2.2 Hz, 1H), 7.35 (dd, $J$ = 4.9, 0.98 Hz, 1H), 7.29 (dd, $J$ = 8.4, 2.3 Hz, 1H), 7.24 (dd, $J$ = 3.5, 0.98 Hz, 1H), 7.05 (dd, $J$ = 5.1, 3.5 Hz, 1H), 6.79 (d, $J$ = 8.4 Hz, 1H), 5.22 (s, 2H), 4.75 (d, $J$ = 13.3 Hz, 2H), 3.56 (t, $J$ = 4.1 Hz, 4H), 3.00 (t, $J$ = 11.3 Hz, 2H), 2.47 (m, 4H), 2.34 to 2.32 (m, 1H), 1.91 to 1.87 (m, 2H), 1.37 to 1.28 (m, 2H). LRMS: 464.20 (calc) 465.2 (obs).
127	10d		N-(2-amino-5-(thiophen-2-yl)phenyl)-2-ethoxypyrimidine-5-carboxamide	$^1\text{H}$ NMR (DMSO- $d_6$ ) $\delta$ (ppm): 9.83 (s, 1H), 9.13 (s, 2H), 7.46 (d, $J$ = 2.2 Hz, 1H), 7.35 (dd, $J$ = 5.1, 1.2 Hz, 1H), 7.31 (dd, $J$ = 8.4, 2.3 Hz, 1H), 7.24 (dd, $J$ = 3.5, 0.98 Hz, 1H), 7.05 (dd, $J$ = 5.1, 3.5 Hz, 1H), 6.79 (d, $J$ = 8.4 Hz, 1H), 5.30 (s, 2H), 4.45 (q, $J$ = 7.0 Hz, 2H), 1.37 (t, $J$ = 6.8 Hz, 3H). LRMS: 340.10 (calc) 341.17 (obs).

### Example 11a

**N-(2-Amino-5-(thiophen-2-yl)phenyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamide**  
(132)

## Scheme 11

Step 1: Methyl 2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxylate (129)

[0732] A solution of hydroxyaniline **128** (1.085 g, 6.49 mmol) and carbonyl diimidazole (1.409 g, 8.69 mmol) in pyridine (3 mL) was stirred at room temperature for 36 h then diluted with AcOEt, washed with 5% KHSO<sub>4</sub> (pH=2), saturated NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give title compound **129** (1.19 g, 95% yield).

[0733] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 7.80 to 7.78 (m, 1H), 7.74 to 7.73 (m, 1H), 7.18 to 7.16 (m, 1H), 3.83 (s, 3H).

Step 2: 2-Oxo-2,3-dihydrobenzo[d]oxazole-6-carboxylic acid (130)

[0734] Following the same procedure as described in Example 10a, step 4 (scheme 10), but substituting compound **122** for compound **129**, acid **130** was obtained (quantitative).

[0735] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 7.78 (dd, *J* = 8.0 Hz, 1H), 7.72 to 7.71 (m, 1H), 7.16 (d, *J* = 8.0 Hz, 1H).

Step 3: *tert*-Butyl 2-(2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamido)-4-(thiophen-2-yl)phenylcarbamate (131)

[0736] Following the same procedure as described in Example 1, step 6 (scheme 1), but substituting compound **7** for compound **130**, intermediate **131** was obtained (99% yield).

[0737] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 9.86 (s, 1H), 8.71 (s, 1H), 7.87 (d, *J* = 1.2 Hz, 1H), 7.82 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.78 (d, *J* = 2.2 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.52 to 7.50 (m, 1H), 7.49 (d, *J* = 2.2 Hz, 1H), 7.44 (dd, *J* = 3.5, 0.98 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.11 (dd, *J* = 5.1, 3.5 Hz, 1H), 1.46 (s, 9H).



Step 4: *N*-(2-Amino-5-(thiophen-2-yl)phenyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamide (**132**)

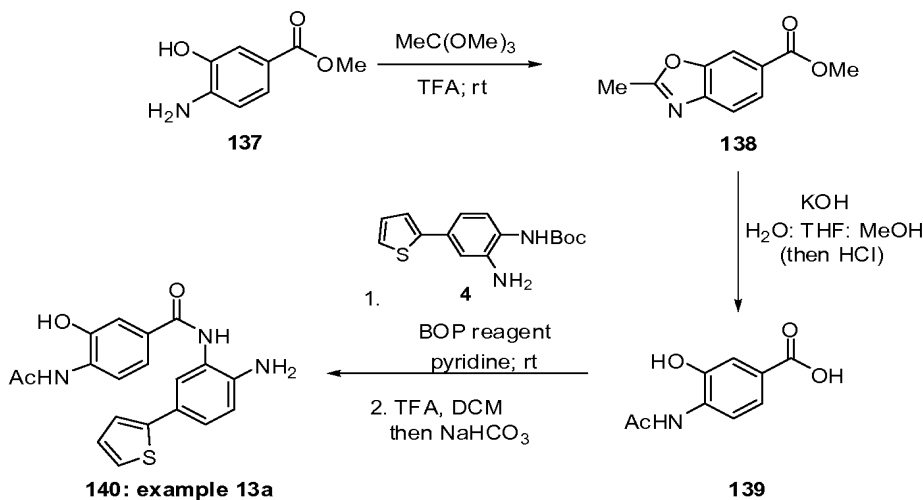
[0738] Following the same procedure as described in Example 1, Step 7 (scheme 1), but substituting compound **8** for compound 131, the title compound **132** was obtained (89% yield).

[0739]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 11.95 (s, 1H), 9.67 (s, 1H), 7.91 (s, 1H), 7.85 (d,  $J$ = 6.5 Hz, 1H), 7.43 (s, 1H), 7.34 (d,  $J$ = 3.7 Hz, 1H), 7.28 (d,  $J$ = 6.5 Hz, 1H), 7.23 (s, 1H), 7.18 (d,  $J$ = 7.8 Hz, 1H), 7.03 (s, 1H), 6.79 (d,  $J$ = 8.0 Hz, 1H), 5.17 (s, 2H). LRMS: 351.4 (calc) 352.1 (obs).

**Example 13a**

**4-Acetamido-*N*-(2-amino-5-(thiophen-2-yl)phenyl)-3-hydroxybenzamide (**140**)**

**Scheme 13**



Step 1: Methyl 2-methylbenzo[d]oxazole-6-carboxylate (**138**)

[0740] A solution of hydroxylamine **137** (0.805 g, 4.815 mmol) was dissolved in trimethyl orthoacetate ( $\text{MeC(OMe)}_3$ ) (10 mL, 78.55 mmol) was treated with TFA (0.6 mL, 7.8 mmol) then stirred at room temperature for 90 min. The reaction mixture was diluted with DCM, washed with saturated  $\text{NaHCO}_3$ , brine, dried over  $\text{MgSO}_4$  and concentrated to give compound **138** (0.911 g, 99% yield).

[0741]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 8.19 (s,  $J$ = 0.98 Hz, 1H), 7.95 (dd,  $J$ = 8.4, 1.6 Hz, 1H), 7.76 (d,  $J$ = 8.2 Hz, 1H), 3.88 (s, 3H), 2.67 (s, 3H).

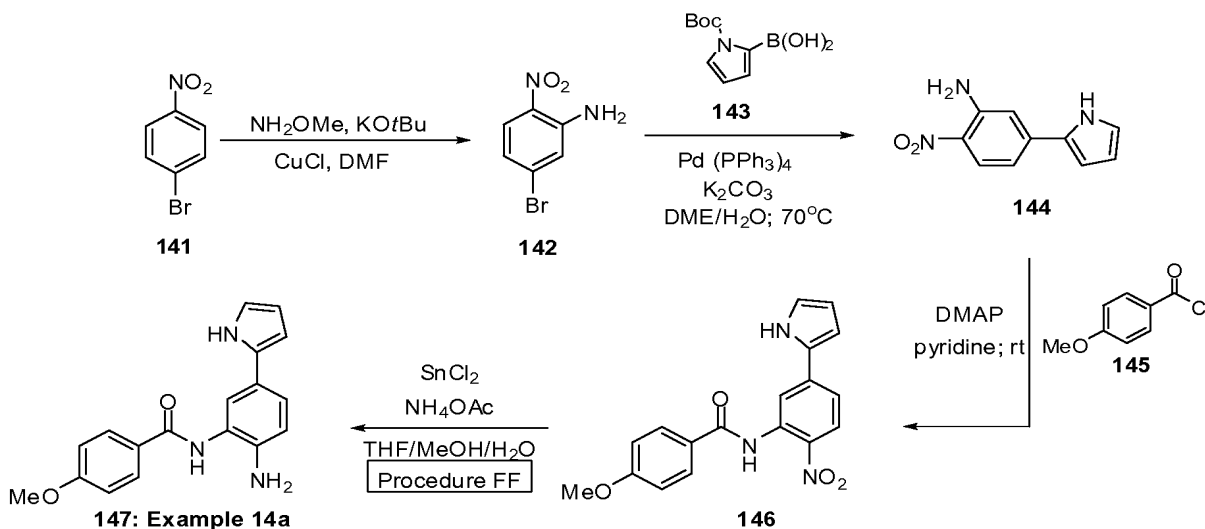
Step 2: 2-Methylbenzo[d]oxazole-6-carboxylic acid (**139**)

[0742] A solution of compound **138** (920 mg, 4.815 mmol) in THF: MeOH (30 mL of a 1:1 solution) was treated with a solution of potassium hydroxide (0.698 g, 17.86 mmol) in H<sub>2</sub>O (15 mL). The reaction mixture was stirred for 65 min at room temperature then quenched with 1N HCl (18 mL, 18.6 mmol) (final pH of 2.5), THF was removed under reduced pressure and the remaining aqueous solution was cooled to -78 °C and lyophilized to give compound **139** (940 mg, quantitative).

Steps 3 & 4: *N*-(2-Amino-5-(thiophen-2-yl)phenyl)-2-methylbenzo[d]oxazole-6-carboxamide (**140**)

[0743] Following the same procedure as described in Example 1, steps 6 and 7 (scheme 1) but substituting compounds 7 for compounds 139, the title compound **140** was obtained in 48% yield (combined for the steps 2-4).

[0744] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 10.16 (s, 1H), 9.59 (s, 1H), 9.38 (s, 1H), 7.97 (d, *J*= 8.6 Hz, 1H), 7.46 to 7.44 (m, 3H), 7.34 (dd, *J*= 5.1, 1.2 Hz, 1H), 7.27 (dd, *J*= 8.2, 2.2 Hz, 1H), 7.23 (dd, *J*= 3.5, 1.2 Hz, 1H), 7.05 to 7.02 (m, 1H), 6.79 (d, *J*= 8.4 Hz, 1H), 5.13 (s, 2H), 3.34 (s, 3H). LRMS: 367.4 (calc) 368.1 (obs).

**Example 14a*****N*-(2-Amino-5-(1*H*-pyrrol-2-yl)phenyl)-4-methoxybenzamide (**147**)****Scheme 14**

Step 1: 5-Bromo-2-nitrobenzenamine (142)

[0745] To a solution of potassium *tert*-butoxide (21.92 g, 195 mmol) and copper (I) chloride (2.36 g, 23.8 mmol) in ethyleneglycol dimethylether (170 mL), stirred at 0 °C under nitrogen, a solution of 1-bromo-4-nitrobenzene (**141**, 8.69 g, 43.0 mmol) in DMF (45 mL) was added drop wise over 50 min. After complete addition the cooling bath was removed and the mixture was allowed to stir at room temperature for 4 h, diluted with DCM, washed with aqueous NH<sub>4</sub>Cl, dried over MgSO<sub>4</sub>, filtered and concentrated to give compound 142 (7.85 g, 84% yield).

[0746] <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ (ppm): 7.98 (d, J= 9.2 Hz, 1H), 7.02 (d, J= 2.0 Hz, 1H), 6.82 (dd, J= 9.2, 2.0 Hz, 1H), 6.12 (bs, 2H).

Step 2: 2-Nitro-5-(1H-pyrrol-2-yl)benzenamine (144)

[0747] Following the same procedure as described in Example 1, step 2 (scheme 1), but substituting compound 2 for compound 142 and 2-thiophene boronic acid for the compound 143, compound 144 was obtained in 10% yield.

[0748] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 11.54 (s, 1H), 7.93 (d, J= 9.0 Hz, 1H), 7.37 (s, 2H), 7.11 (d, J= 1.8 Hz, 1H), 6.98 to 6.96 (m, 1H), 6.92 (dd, J= 9.2, 1.9 Hz, 1H), 6.61 to 6.59 (m, 1H), 6.19 to 6.17 (m, 1H).

Step 3: 4-Methoxy-N-(2-nitro-5-(1H-pyrrol-2-yl)phenyl)benzamide (146)

[0749] A solution of 4-methoxybenzoyl chloride (**145**, 0.175 g, 1.0 mmol), aniline **144** (79.2 mg, 0.39 mmol) and 4-(dimethylamino)pyridine (catalytic amount) was stirred at room temperature for 24 h. The reaction mixture was diluted with DCM, treated with saturated NaHCO<sub>3</sub>, stirred for 3 h and diluted with AcOEt. Organic phase was collected, washed with saturated NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered and concentrated to provide compound 146 (0.133 g, 100% yield).

[0750] MS: 337.33 (calc) 338.0 (obs)

Step 4: N-(2-Amino-5-(1H-pyrrol-2-yl)phenyl)-4-methoxybenzamide (147)

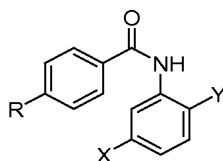
[0751] A solution of nitro compound 146 (0.1326 g, 0.39 mmol) in a 8.5: 5: 1 mixture of THF: MeOH: H<sub>2</sub>O (14.5 mL) was treated with tin(II) chloride dihydrate (0.602 g, 2.67 mmol) and ammonium acetate (0.818 g, 10.6 mmol) then heated to 55 °C for 60 min. The reaction mixture was cooled to room temperature, diluted with AcOEt, washed with 5% KHSO<sub>4</sub>, saturated NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The title compound 147

was obtained after purification by chromatotron (14.7 mg, 12% yield, eluent: 50% AcOEt in hexane).

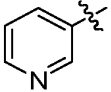
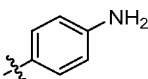
**[0752]** Alternative method. Following the same procedure as described in Example 1, step 3 (scheme 1) but substituting compound **3** for compound **146**, the title compound can be obtained.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 10.94 (s, 1H), 9.60 (s, 1H), 7.97 (d, J= 8.8 Hz, 2H), 7.38 (d, J= 1.8 Hz, 1H), 7.23 (dd, J= 8.4, 2.2 Hz, 1H), 7.03 (d, J= 8.8 Hz, 2H), 6.75 (d, J= 8.4 Hz, 1H), 6.69 to 6.67 (m, 1H), 6.23 to 6.21 (m, 1H), 6.02 to 6.00 (m, 1H), 4.85 (s, 2H), 3.83 (s, 3H). LRMS: 307.3 (calc) 308.3 (obs).

Table 10: Characterization of compounds prepared according to Scheme 14



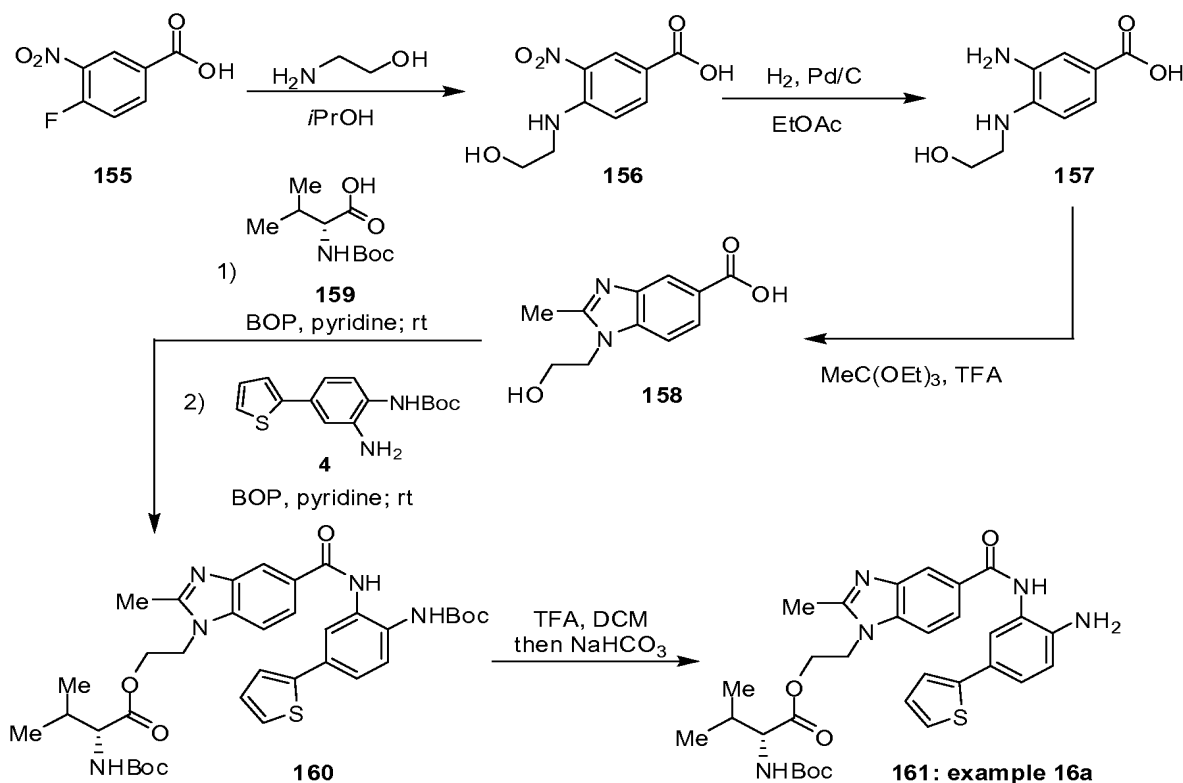
Cpd	Ex	R	X	Y	Name	Characterization
<b>148</b>	<b>14b</b>			NH <sub>2</sub>	N-(2-amino-5-(1H-pyrrol-2-yl)phenyl)-4-(pyridin-3-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.96 (s, 1H), 9.81 (s, 1H), 8.98 (d, J= 1.6 Hz, 1H), 8.60 (dd, J= 4.7, 1.6 Hz, 1H), 8.19 to 8.16 (m, 1H), 8.12 (d, J= 8.0 Hz, 2H), 7.90 (d, J= 8.4 Hz, 2H), 7.52 (dd, J= 7.8, 4.7 Hz, 1H), 7.42 (s, 1H), 7.26 (dd, J= 8.2, 2.0 Hz, 1H), 6.77 (d, J= 8.2 Hz, 1H), 6.69 to 6.68 (m, 1H), 6.23 to 6.01 (m, 1H), 4.92 (s, 2H). LRMS: 354.4 (calc) 355.2 (obs).
<b>149</b>	<b>14c</b>			NH <sub>2</sub>	N-(2-amino-5-(1H-pyrazol-4-yl)phenyl)-4-(pyridin-3-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 8.99 (d, J= 2.0 Hz, 1H), 8.63 (dd, J= 4.7, 1.6 Hz, 1H), 8.59 (s, 1H), 8.22 (d, J= 0.6 Hz, 1H), 8.20 to 8.17 (m, 1H), 8.14 (d, J= 8.2 Hz, 2H), 7.93 (d, J= 8.2 Hz, 2H), 7.56 to 7.52 (m, 1H), 6.89 (d, J= 2.0 Hz, 1H), 6.85 to 6.83 (m, 1H), 6.53 (d, J= 7.8 Hz, 1H), 4.69 (s, 2H), 4.54 (s, 1H), 1.04 (d, J= 6.0 Hz, 1H). LRMS: 355.4 (calc) 356.3 (obs).

Cpd	Ex	R	X	Y	Name	Characterization
150	14d			NH <sub>2</sub>	N-(4,4'-diaminobiphenyl-1-yl)-4-(pyridin-3-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.80 (s, 1H), 8.98 (d, J= 1.4 Hz, 1H), 8.60 (dd, J= 4.7, 1.6 Hz, 1H), 8.18 to 8.16 (m, 1H), 8.12 (d, J= 8.2 Hz, 2H), 7.89 (d, J= 8.4 Hz, 2H), 7.54 to 7.50 (m, 1H), 7.38 (s, 1H), 7.22 (d, J= 8.4 Hz, 2H), 7.18 (dd, J= 8.2, 2.0 Hz, 1H), 6.80 (d, J= 8.4 Hz, 1H), 6.58 (d, J= 8.6 Hz, 2H), 5.05 (s, 2H), 4.92 (d, 2H). LRMS: 380.44 (calc) 381.2 (obs).

### Example 16a

(S)-2-(5-(2-Amino-5-(thiophen-2-yl)phenylcarbamoyl)-2-methyl-1*H*-benzo[d]imidazol-1-yl)ethyl 2-(tert-butoxycarbonylamino)-3-methylbutanoate (161)

### Scheme 16



#### Step 1: 4-(2-Hydroxyethylamino)-3-nitrobenzoic acid (**156**)

[0753] A solution of fluoride **155** (1.13 g, 6.08 mmol) in isopropanol (12 mL) was treated with neat ethanolamine (3.0 mL, 49.7 mmol) added dropwise then it was stirred at room temperature for 18 h. The reaction mixture was suspended in AcOEt and washed with 5%

KHSO<sub>4</sub>, brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give intermediate 156 (1.334 g, 97% yield).

[0754] LRMS: 226.2 (calc) 225.1 (obs, M-H)

Step 2: 3-Amino-4-(2-hydroxyethylamino)benzoic acid (157)

[0755] A solution of intermediate **156** (1.33 g, 5.9 mmol) in AcOEt/MeOH was stirred under H<sub>2</sub> in the presence of 10% palladium on carbon for 18 h, filtered through Celite®, concentrated and then triturated with DCM to give compound 157 (1.18 g, >99% yield).

[0756] LRMS: 196.2 (calc) 197.1 (obs)

Step 3: 1-(2-Hydroxyethyl)-2-methyl-1H-benzo[d]imidazole-5-carboxylic acid (158)

[0757] Following the same procedure as described in Example 13, step 1 (scheme 13), but substituting compound **137** for compound **157**, title compound **158** was obtained (0.701 g, 53% yield) after purification by preparative HPLC [Gilson, column aquasil C18 (5µM), 250 x 21.2 mm; gradient 10% to 80% MeOH in water, UV detection)].

Steps 4 & 5: (R)-2-(5-(2-(tert-Butoxycarbonylamino)-5-(thiophen-2-yl)phenylcarbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)ethyl 2-(tert-butoxycarbonylamino)-3-methylbutanoate (160)

[0758] Following the same procedure as described in Example 1, step 6 (scheme 1), but substituting compound **4** for compound **158** and compound **7** for compound **159**, an ester intermediate was obtained (structure not shown in the scheme 16). Following the same procedure as described in Example 1, step 6 (scheme 1), but substituting compound **7** for the above mentioned ester intermediate, compound **160** was obtained (19% yield over two steps) after purification by chromatotron (eluent: 5% iso-PrOH in DCM).

[0759] LRMS: 691.84 (calc) 692.5 (obs).

Step 6: (R)-2-(5-(2-Amino-5-(thiophen-2-yl)phenylcarbamoyl)-2-methyl-1H-benzo[d]imidazol-1-yl)ethyl 2-(tert-butoxycarbonylamino)-3-methylbutanoate (161)

[0760] Following the same procedure as described in Example 1, step 7 (scheme 1), but substituting compound **8** for compound 160, title compound 161 was obtained (84% yield).

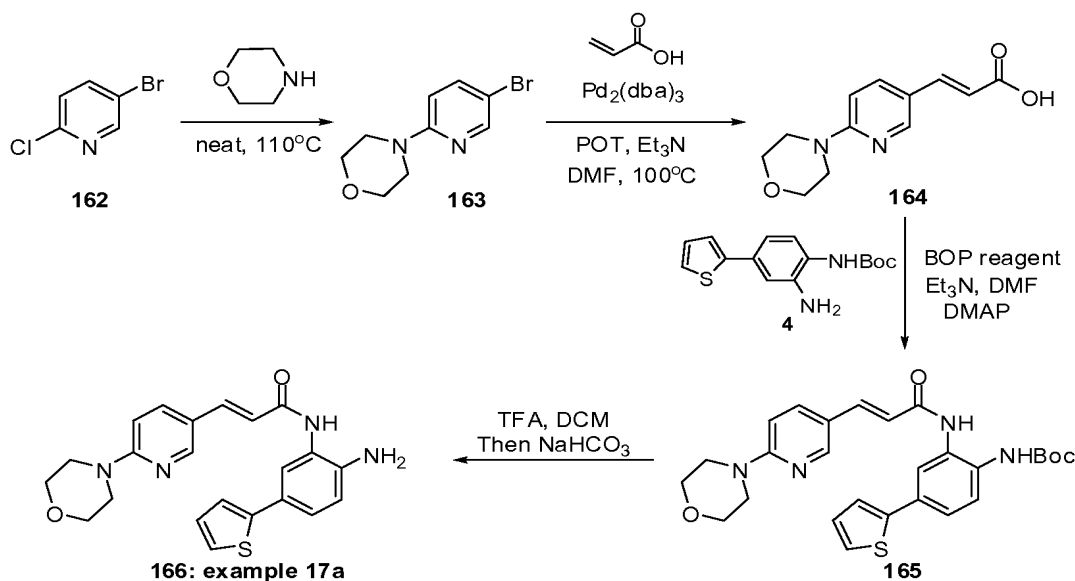
[0761] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.70 (s, 1H), 8.23 (s, 1H), 7.88 (d, J= 1.6 Hz, 1H), 7.86 (d, J= 1.6 Hz, 1H), 7.65 (d, J= 8.0 Hz, 1H), 7.48 (d, J= 2.2 Hz, 1H), 7.34 (dd, J= 5.1, 1.2 Hz, 1H), 7.28 (dd, J= 8.2, 2.2 Hz, 1H), 7.24 (dd, J= 3.5, 1.2 Hz, 1H), 7.04 (dd, J= 5.1, 3.5 Hz, 1H), 6.81 (d, J= 8.2 Hz, 1H), 5.14 (s, 2H), 4.55 (d, J= 4.9 Hz, 2H), 4.38 (d, J= 4.5 Hz, 2H), 2.99 (d, J=

5.3 Hz, 1H), 2.61 (s, 3H), 1.68 to 1.63 (m, 2H), 0.71 (d, J= 6.8 Hz, 3H), 0.64 (d, J= 6.8 Hz, 3H). LRMS: 491.6 (calc) 492.4 (obs).

### Example 17a

#### (E)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-3-(6-morpholinopyridin-3-yl)acrylamide (166)

#### Scheme 17



#### Step 1: 4-(5-Bromopyridin-2-yl)morpholine (**163**)

[0762] Following the same procedure as described in Example 3, step 3 (scheme 3), but substituting N-methylpiperazine for morpholine and compound 46 for compound 162, title compound 163 was obtained in 57% yield.

[0763] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 8.13 (d, J= 2.2 Hz, 1H), 7.63 (dd, J= 9.0, 2.5 Hz, 1H), 6.74 (d, J= 9.0 Hz, 1H), 3.76 (t, J= 4.7 Hz, 4H), 3.45 (t, J= 4.9 Hz, 4H). LRMS: 243.10 (calc) 243.0/245.0 (obs).

#### Step 2: (E)-3-(6-Morpholinopyridin-3-yl)acrylic acid (**164**)

[0764] Following the same procedure as described in Example 2, step 2 (scheme 2), but substituting compound 37 for compound 163, and compound 38 for acrylic acid, title compound 164 was obtained (41% yield).

[0765] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 12.14 (bs, 1H), 8.32 (d, J= 2.3 Hz, 1H), 7.92 (dd, J= 9.2, 2.5 Hz, 1H), 7.47 (d, J= 15.8 Hz, 1H), 6.85 (d, J= 9.0 Hz, 1H), 6.33 (d, J= 15.8 Hz, 1H), 3.67 to 3.65 (m, 4H), 3.54 to 3.52 (m, 4H). LRMS: 234.27 (calc) 235.1 (obs).

Step 3: (E)-tert-Butyl 2-(3-(6-morpholinopyridin-3-yl)acrylamido)-4-(thiophen-2-yl)phenylcarbamate (165)

[0766] To a solution of **164** (0.275 g, 1.17 mmol) in DMF (10 mL) was added triethylamine (0.168 mL, 1.21 mmol) and BOP reagent (0.563 g, 1.27 mmol) and the mixture was stirred at room temperature for 30 min. Then amine **4** (0.309 g, 1.06 mmol) and excess triethylamine (0.443 mL, 3.18 mmol) were added and the reaction mixture was allowed to stir for 18 h at room temperature. Then 4-(dimethylamino)pyridine (catalytic amount) was added and the reaction mixture was heated to 50-60 °C for 24 h. The solution was concentrated, diluted with AcOEt, washed with saturated NaHCO<sub>3</sub>, H<sub>2</sub>O, brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The resulting yellow solid was triturated from ethyl ether to give compound **165** (0.435 g, 81% yield).

[0767] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.68 (s, 1H), 8.58 (bs, 1H), 8.35 (d, J= 2.3 Hz, 1H), 7.85 (d, J= 2.0 Hz, 1H), 7.82 (d, J= 2.0 Hz, 1H), 7.61 (d, J= 9.0 Hz, 1H), 7.52 (d, J= 15.5 Hz, 1H), 7.51 (dd, J= 5.1, 1.2 Hz, 1H), 7.44 (dd, J= 8.4, 2.3 Hz, 1H), 7.41 (dd, J= 3.5, 1.2 Hz, 1H), 7.11 (dd, J= 5.1, 3.5 Hz, 1H), 6.92 (d, J= 9.4 Hz, 1H), 6.71 (d, J= 15.4 Hz, 1H), 4.02 to 3.97 (m, 4H), 3.69 to 3.67 (m, 4H), 1.45 (s, 9H). LRMS: 506.62 (calc) 507.1 (obs).

Step 4: (E)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-3-(6-morpholinopyridin-3-yl)acrylamide (166)

[0768] Following the same procedure as described in Example 1, step 7 (scheme 1), but substituting compound **8** for compound **165**, the title compound **166** was obtained in 92% yield.

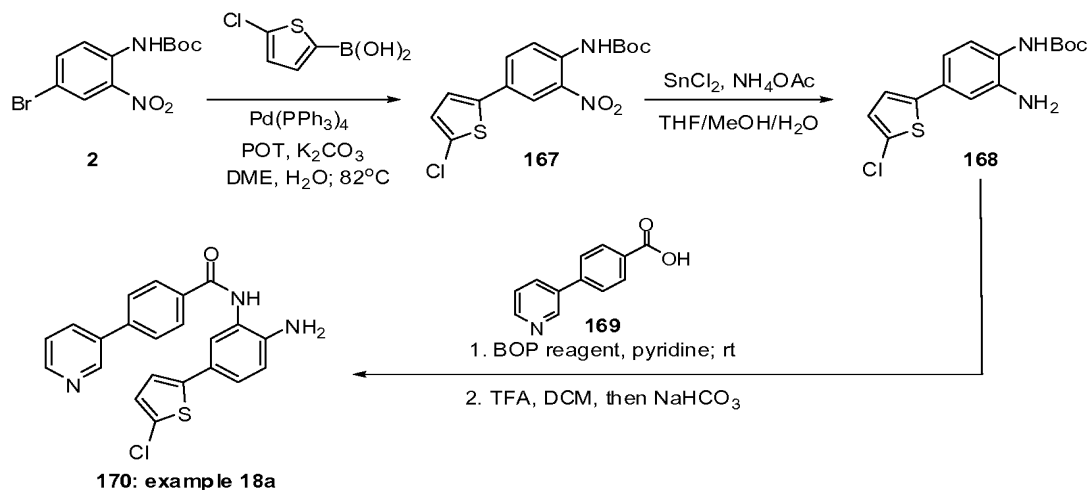
[0769] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.33 (s, 1H), 8.33 (d, J=2.0 Hz, 1H), 7.80 (dd, J=8.8, 2.5 Hz, 1H), 7.66 (d, J=1.8 Hz, 1H), 7.48 (d, J=15.4 Hz, 1H), 7.34 (dd, J=5.1, 1.0 Hz, 1H), 7.22 (dd, 9.0, 2.2 Hz, 1H), 7.20 (dd, J=3.5, 1.2 Hz, 1H), 7.03 (d, J=5.1, 3.5 Hz, 1H), 6.92 (d, J=9.0 Hz, 1H), 6.76 (d, J=8.4 Hz, 1H), 6.70 (d, J=15.7 Hz, 1H), 5.18 (s, 2H), 3.69-3.66 (m, 4H), 3.54-3.51 (m, 4H). LRMS: 406.51 (calc) 407.1 (obs).

**Example 18a**

**N-(2-Amino-5-(5-chlorothiophen-2-yl)phenyl)-4-(pyridin-3-yl)benzamide (170)**



## Scheme 18

Step 1: *tert*-Butyl 4-(5-chlorothiophen-2-yl)-2-nitrophenylcarbamate (**167**)

[0770] Following the same procedure as described in Example 1, step 2 (scheme 1), but substituting 2-thiophene boronic acid for 5-chloro-2-thiophene boronic acid, title compound 167 was obtained after purification by column chromatography (45% yield, eluent: 5% isopropanol in DCM).

[0771] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 9.67 (s, 1H), 8.10 (s, *J* = 2.2 Hz, 1H), 7.88 to 7.85 (m, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.51 (d, *J* = 3.9 Hz, 1H), 7.19 (d, *J* = 3.9 Hz, 1H), 1.45 (s, 9H).  
LRMS: 354.04 (calc) 377.0 (obs *M*+Na).

Step 2: *tert*-Butyl 2-amino-4-(5-chlorothiophen-2-yl)phenylcarbamate (**168**)

[0772] Following the same procedure as described in Example 14, step 4 (scheme 14), but substituting compound 146 for compound 167, title compound 168 was obtained in quantitative yield.

[0773] LRMS: 268.01 (calc *M*-*t*Bu) 269.0 (obs *M*-*t*Bu).

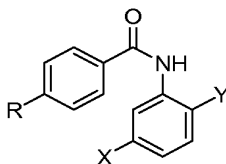
Steps 3 & 4: *N*-(2-Amino-5-(5-chlorothiophen-2-yl)phenyl)-4-(pyridin-3-yl)benzamide (**170**)

[0774] Following the same procedure as described in Example 1, steps 6 & 7 (scheme 1), but substituting compounds 4 and 7 for compounds 168 and 169 respectively, the title compound 170 was obtained in 76% yield (purified by column chromatography, eluent: 5 to 10% isopropanol in DCM).

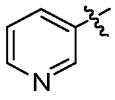
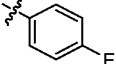
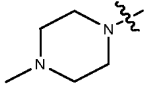
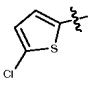
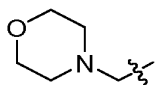
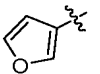
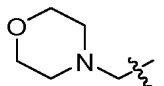
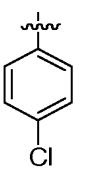
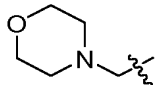
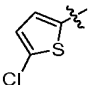
[0775] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 9.80 (s, 1H), 8.98 (d, *J* = 2.3 Hz, 1H), 8.60 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.17 (dt, *J* = 8.0, 1.6 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.52

(dd, J= 7.8, 4.7 Hz, 1H), 7.42 (d, J= 2.0 Hz, 1H), 7.24 (dd, J= 8.2, 2.2 Hz, 1H), 7.11 (d, J= 3.9 Hz, 1H), 7.04 (d, J= 3.9 Hz, 1H), 6.80 (d, J= 8.2 Hz, 1H), 5.29 (s, 2H). LRMS: 405.1 (calc) 406.1 (obs).

Table 11: Characterization of compound prepared according to Scheme 18



Cpd	Ex	R	X	Y	Name	Characterization
171	18b			NH <sub>2</sub>	N-(4-aminobiphenyl-1-yl)-4-(pyridin-3-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.48 (s, 1H), 9.15 (s, 1H), 8.74 (d, 1H, J=5.1 Hz), 8.52 (d, 1H, J=7.8Hz), 8.26 (d, 2H, J=8.2Hz), 7.98 (d, 2H, J=8.4Hz), 7.80 (d, 2H, J=8.2Hz), 7.62 (d, 2H, J=7.2Hz), 7.51 (d, 1H, J=8.4Hz), 7.44 (t, 2H, J=7.4Hz), 7.32 (t, 2H, J=7.2Hz). LRMS: 365.43 (calc) 366.3 and 183.6 (obs).
172	18c			CO <sub>2</sub> H	2-(4-((6-chloro-5-fluoro-1H-benzo[d]imidazol-2-ylthio)methyl)benzamido)-4-(thiophen-2-yl)benzoic acid	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 12.91 (d, J= 12.5 Hz, 1H), 12.33 (s, 1H), 9.05 (s, 1H), 8.04 (d, J= 8.2 Hz, 1H), 7.89 (d, J= 7.8 Hz, 2H), 7.74 to 7.51 (m, 6H), 7.19 (s, 1H), 4.65 (s, 2H). LRMS: 537.04 (calc), 538.2 (obs).
173	18d			NH <sub>2</sub>	N-(2-amino-5-(pyridin-3-yl)phenyl)-4-(pyridin-3-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.83 (s, 1H), 8.97 (s, 1H), 8.78 (s, 1H), 8.60 (s, 1H), 8.42 (s, 1H), 8.17 (d, J=7.6 Hz, 1H), 8.13 (d, J=8.0 Hz, 2H), 7.94 (d, J=8.6 Hz, 1H), 7.90 (d, J=8.6 Hz, 2H), 7.58 (s, 1H), 7.52 (dd, J=8.0, 4.5 Hz, 1H), 7.40 (d, J=7.6 Hz, 2H), 6.89 (d, J=8.2 Hz, 1H), 5.25 (d, J=0.4 Hz, 2H). LRMS: 366.42 (calc) 367.3 (obs).

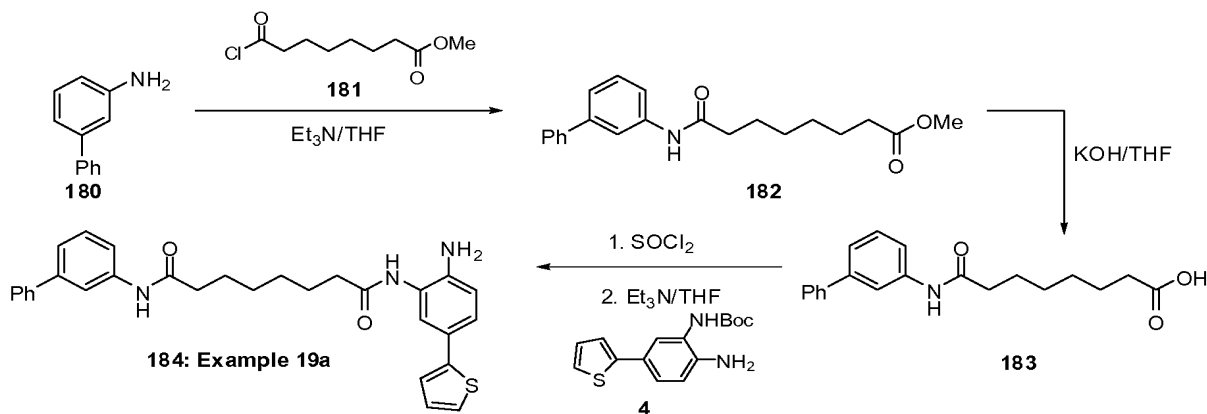
Cpd	Ex	R	X	Y	Name	Characterization
174	18e			NH <sub>2</sub>	N-(4-amino-4'-fluorobiphenyl-1-yl)-4-(pyridin-3-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.80 (s, 1H), 8.98 (d, J=1.57 Hz, 1H), 8.60 (dd, J=4.5, 1.4 Hz, 1H), 8.17 (d, J=7.8 Hz, 1H), 8.12 (d, J=8.2 Hz, 2H), 7.89 (d, J=8.6 Hz, 2H), 7.62 (m, 6H), 7.30 (dd, J=10.6, 8.4 Hz, 1H), 7.20 (t, J=8.8 Hz, 2H), 6.85 (d, J=8.02 Hz, 1H), 5.14 (s, 2H). LRMS: 383.42 (calc) 384.2 (obs).
175	18f			NH <sub>2</sub>	N-(2-amino-5-(5-chlorothiophen-2-yl)phenyl)-4-(4-methylpiperazin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.50 (s, 1H), 7.88 (d, J= 9.0 Hz, 2H), 7.40 (d, J= 2.2 Hz, 1H), 7.22 (dd, J= 8.4, 2.3 Hz, 1H), 7.11 (d, J= 3.9 Hz, 1H), 7.05 (d, J= 3.9 Hz, 1H), 7.01 (d, J= 9.2 Hz, 2H), 6.80 (d, J= 8.4 Hz, 1H), 5.19 (s, 2H), 3.28 (t, J= 4.7 Hz, 4H), 2.45 (t, J= 4.9 Hz, 4H), 2.22 (s, 3H). LRMS: 426.1 (calc) 427.0 (obs).
176	18g			NH <sub>2</sub>	N-(2-amino-5-(furan-3-yl)phenyl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 7.92 (s, 1H), 7.88 (d, J=8.0 Hz, 2H), 7.63 (s, 1H), 7.44 (m, 3H), 7.22 (dd, J=7.9, 2.2 Hz, 1H), 6.85 (d, J=8.1 Hz, 1H), 6.62 (s, 1H), 3.91 (b, 2H), 3.72 (t, J=5.1 Hz, 4H), 3.57 (s, 2H), 2.43 (t, J=5.2 Hz, 4H), 1.62 (s, 1H). LRMS: 377.4 (calc) 378.1 (obs)
177	18h			NH <sub>2</sub>	N-(4-amino-4'-chlorobiphenyl-1-yl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 7.88 (m, 3H), 7.42 (m, 6H), 6.90 (d, J=8.1 Hz, 1H), 3.92 (s, 2H), 3.72 (t, J=5.1 Hz, 4H), 3.57 (s, 2H), 2.42 (t, J=5.1 Hz, 4H), 1.64 (s, 1H). LRMS: 421.1 (calc) 422.1 (obs).
178	18i			NH <sub>2</sub>	N-(2-amino-5-(5-chlorothiophen-2-yl)phenyl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.71 (s, 1H), 7.92 (d, J=8.7 Hz, 2H), 7.42 (d, J=8.1 Hz, 2H), 7.31 (s, 1H), 7.22 (m, 1H), 7.07 (dd, J=23.0, 4.1 Hz, 2H), 6.81 (d, J=9.1 Hz, 1H), 5.22 (s, 2H), 3.58 (t, J=3.4 Hz, 4H), 3.51 (s, 2H), 2.70 (s, 4H). LRMS: 427.95 (calc) 428.0 (obs).

Cpd	Ex	R	X	Y	Name	Characterization
179	18j			NH <sub>2</sub>	N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(1'1'-dioxothiomorpholinomethyl)benzamide	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 9.76 (s, 1H), 7.98 (d, J=8.0 Hz, 2H), 7.48 (d, J=8.2 Hz, 2H), 7.46 (d, J=2.0 Hz, 1H), 7.35 (dd, J=5.1, 1.2 Hz, 1H), 7.30 (dd, J=8.4, 2.3 Hz, 1H), 7.24 (dd, J=3.5, 1.0 Hz, 1H), 7.04 (dd, J=5.1, 3.5 Hz, 1H), 6.82 (d, J=8.4 Hz, 1H), 3.81 (s, 2H), 3.15 (bs, 4H), 2.93 (bs, 4H). LRMS: 441.57 (calc) 442.0 (obs).

### Example 19a

#### N1-(2-Amino-5-(thiophen-2-yl)phenyl)-N8-(biphenyl-3-yl)octanediamide (184)

#### Scheme 19



#### Step 1: Methyl 8-(biphenyl-3-ylamino)-8-oxooctanoate (182)

[0776] A solution of biphenyl-3-amine (**180**) (0.171 g, 1.01 mmol) in THF (3 mL) was cooled to 0 °C then treated with methyl 8-chloro-8-oxooctanoate (**181**) and stirred for 2 h. The reaction mixture was then diluted with AcOEt, washed with saturated NH<sub>4</sub>Cl, dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by flash chromatography (eluent: 30 to 40% AcOEt in hexane), to provide title compound **182** (0.212 g, 69% yield).

[0777] LRMS: 339.18 (calc) 340.3 (obs).

#### Step 2: 8-(Biphenyl-3-ylamino)-8-oxooctanoic acid (183)

[0778] A solution of compound **182** (0.212 g, 0.62 mmol) in THF (10 mL) was treated with potassium hydroxide (5 mL of a 3.5% aqueous solution) and stirred at room temperature for 72 h then concentrated, diluted with diethyl ether and acidified with citric acid. The acidic mixture was extracted with AcOEt, washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, filtered, and concentrated to give title compound **183** (0.182 g, 90% yield).

[0779] LRMS: 325.17 (calc) 326.1 (obs).

Step 3: *N*1-(2-Amino-5-(thiophen-2-yl)phenyl)-*N*8-(biphenyl-3-yl)octanediamide (184)

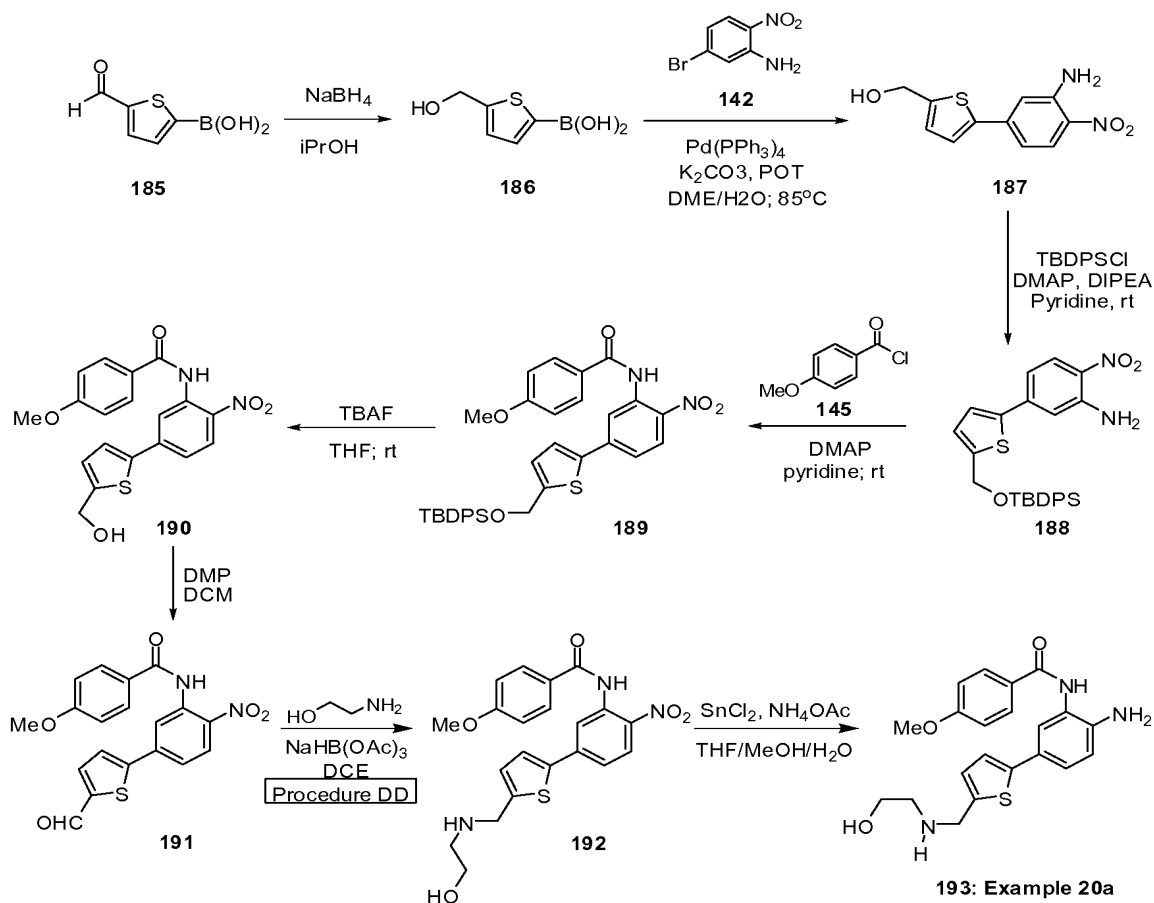
[0780] Acid 183 (0.103 g, 0.32 mmol) in thionyl chloride (3 mL) with a few drops of DMF was stirred at room temperature for 15 min then concentrated, diluted with dry THF (10 mL), cooled to 0 °C then treated with amine **4** (0.12 g, 0.41 mmol) and triethylamine (0.086 mL, 0.61 mmol). The reaction mixture was stirred at 0 °C for 30 min then quenched with aqueous NH<sub>4</sub>Cl, extracted with AcOEt, dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by flash chromatography (eluent: 50% AcOEt - hexane) to give the title compound 184 (0.111 g, 52% yield).

[0781] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ(ppm): 9.97 (s, 1H), 9.14 (s, 1H), 7.59 to 7.55 (m, 3H), 7.48 to 7.43 (m, 3H), 7.38 to 7.30 (m, 4H), 7.21 to 7.17 (m, 2H), 7.01 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 5.06 (s, 2H), 2.32 (t, *J* = 7.6 Hz, 4H), 1.61 (m, 4H), 1.35 (m, 4H). LRMS: 497.21 (calc) 498.4 (obs).

#### Example 20a

***N*-(2-Amino-5-(5-((2-hydroxyethylamino)methyl)thiophen-2-yl)phenyl)-4-methoxybenzamide (193)**

Scheme 20



#### Step 1: 5-(Hydroxymethyl)thiophen-2-ylboronic acid (186)

[0782] A suspension of 5-formylthiophen-2-ylboronic acid **185** (1.096 g, 7.03 mmol) in isopropanol (10 mL), stirred at 0 °C, was treated with solid sodium borohydride (0.336 g, 8.88 mmol) added portion-wise at 0 °C then stirred for 75 min. The reaction was quenched with acetone and concentrated to give compound 186 (used directly in Step 2).

[0783] LRMS: 158.0 (calc) 159.1 (obs).

#### Step 2: (5-(3-Amino-4-nitrophenyl)thiophen-2-yl)MeOH (187)

[0784] Following the same procedure as described in Example 1, step 2 (scheme 1), but substituting 2-thiophene boronic acid for 5-(hydroxymethyl)thiophen-2-ylboronic acid (186) and bromoarene 2 for 5-bromo-2-nitrobenzenamine (142), intermediate 187 was obtained after purification by column chromatography (84% yield, eluent: 40 to 60% AcOEt in hexane).

[0785] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 7.96 (d, 9.0 Hz, 1H), 7.49 (s, 2H), 7.44 (d, J= 3.7 Hz, 1H), 7.21 (d, J= 2.0 Hz, 1H), 6.99 (dt, J= 3.7, 0.98 Hz, 1H), 6.94 (dd, J= 9.0, 2.2 Hz, 1H), 5.61 (t, J= 5.8 Hz, 1H), 4.65 (dd, J= 5.7, 0.78 Hz, 2H). LRMS: 250.3 (calc) 251.0 (obs).

Step 3: 5-(5-((*tert*-Butyldiphenylsilyloxy)methyl)thiophen-2-yl)-2-nitrobenzenamine (188)

[0786] A solution of alcohol **187** (1.217 g, 4.86 mmol), DMAP (catalytic amount) and diisopropylethylamine (1 mL) in pyridine (10 mL) was treated with neat *tert*-butyldiphenylsilylchloride (1.5 mL, 5.74 mmol) and the mixture was stirred under nitrogen atmosphere for 18 h at room temperature. The reaction mixture was diluted with AcOEt then washed with 5% KHSO<sub>4</sub>, saturated NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give compound **188** (1.75 g, 74% yield).

[0787] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 7.97 (d, J= 9.0 Hz, 1H), 7.66-7.64 (m, 4H), 7.51 to 7.50 (m, 2H), 7.48-7.44 (m, 7H), 7.24 (d, J= 2.0 Hz, 1H), 6.98-6.95 (m, 2H), 4.93 (s, 2H), 1.05 (s, 9H). LRMS: 488.7 (calc) 489.2 (obs).

Step 4: *N*-(5-(5-((*tert*-Butyldiphenylsilyloxy)methyl)thiophen-2-yl)-2-nitrophenyl)-4-methoxybenzamide (189)

[0788] Following the same procedure as described in Example 14a, step 3 (scheme 14), but substituting compound 144 for compound 188, the title compound **189** was obtained (97% yield).

[0789] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 10.73 (s, 1H), 8.11 (d, J= 2.0 Hz, 1H), 8.05 (d, J= 8.8 Hz, 1H), 7.95 (d, J= 8.8 Hz, 2H), 7.67-7.64 (m, 5H), 7.58 (d, J= 3.7 Hz, 1H), 7.48-7.42 (m, 6H), 7.10 (d, J= 9.0 Hz, 2H), 7.01 (d, J= 3.7 Hz, 1H), 4.95 (s, 2H), 3.86 (s, 3H), 1.05 (s, 9H).

Step 5: *N*-(5-(5-(Hydroxymethyl)thiophen-2-yl)-2-nitrophenyl)-4-methoxybenzamide (190)

[0790] A solution of compound **189** (0.673 g, 1.08 mmol) in a 1M solution of tetrabutylammonium fluoride in THF (1.5 mL, 1.5 mmol) was stirred for 90 min at room temperature. The reaction mixture was diluted with AcOEt, washed with 5% KHSO<sub>4</sub>, water, dried over MgSO<sub>4</sub>, filtered and concentrated to give a solid material which was triturated with DCM, to afford title compound **190** (0.805 g, 75% yield). The supernatant was collected, evaporated and the residue was purified by flash column chromatography (eluent: 50% AcOEt in DCM) to afford additional amount of **190** (0.161 g, 15% yield).

[0791] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 10.73 (s, 1H), 8.17 (d, J= 2.0 Hz, 1H), 8.05 (d, J= 8.8 Hz, 1H), 7.95 (d, J= 9.0 Hz, 2H), 7.63 (dd, J= 8.8, 2.2 Hz, 1H), 7.57 (d, J= 3.7 Hz, 1H), 7.11 (d,

J= 9.0 Hz, 2H), 7.04 to 7.03 (m, 1H), 5.65 (t, J= 5.7 Hz, 1H), 4.67 (d, J= 5.9 Hz, 2H), 3.86 (s, 3H). LRMS: 384.41 (calc) 407.1 (obs M+Na).

Step 6: *N*-(5-(5-Formylthiophen-2-yl)-2-nitrophenyl)-4-methoxybenzamide (**191**)

[0792] A suspension of alcohol **190** (0.178 g, 0.463 mmol) in DCM (5.0 mL) was treated with solid Dess-Martin periodinane (0.399 g, 0.94 mmol) and stirred under nitrogen atmosphere at room temperature for 20 h. The reaction mixture was quenched with an aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, stirred for 60 min, diluted with DCM/MeOH mixture, washed with saturated NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered and concentrated to give title compound **191** (0.155 g, 88% yield).

[0793] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 10.75 (s, 1H), 9.94 (s, 1H), 8.25 (d, J= 2.0 Hz, 1H), 8.11 to 8.08 (m, 2H), 7.95 (dd, J= 8.8, 1.2 Hz, 2H), 7.91 (dd, J= 3.9, 1.2 Hz, 1H), 7.81 (dd, J= 8.6, 2.2 Hz, 1H), 7.12 to 7.10 (m, 2H), 3.86 (s, 3H). LRMS: 382.39 (calc) 381.0 (obs M-H).

Step 7: *N*-(5-(5-((2-Hydroxyethylamino)methyl)thiophen-2-yl)-2-nitrophenyl)-4-methoxybenzamide (**192**)

[0794] A solution of aldehyde **191** (0.155 g, 0.41 mmol) in 1,2-dichloroethane (3.0 mL) was treated with ethanolamine (0.06 mL, 1 mmol) and the mixture was allowed to stir at room temperature for 6 h. The mixture was then treated with solid NaHB(OAc)<sub>3</sub> (0.354 g, 1.67 mmol), more 1,2-dichloroethane (3 mL) and stirred a further 17 h at room temperature. The mixture was treated with 10% aqueous K<sub>2</sub>CO<sub>3</sub>, extracted with DCM, dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column chromatography (eluent: 5 to 10% isopropanol in DCM with 1% triethylamine then 5 to 10% MeOH in DCM with 1% triethylamine, to give title compound **192** (77.5 mg, 44% yield).

[0795] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 10.74 (s, 1H), 8.21 (d, J= 2.0 Hz, 1H), 8.07 (d, J= 8.6 Hz, 1H), 7.95 (d, J= 9.0 Hz, 2H), 7.66 to 7.61 (m, 2H), 7.17 to 7.10 (m, 3H), 7.80 (m, 1H), 4.13 to 4.10 (m, 2H), 3.86 (s, 3H), 3.55 (q, J= 5.5 Hz, 2H), 2.78 (m, 2H). LRMS: 427.47 (calc) 428.3 (obs).

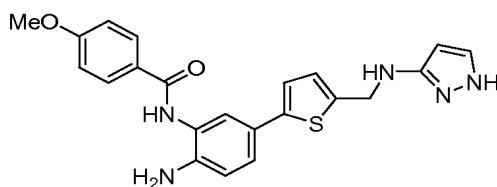
Step 8: *N*-(2-Amino-5-(5-((2-hydroxyethylamino)methyl)thiophen-2-yl)phenyl)-4-methoxybenzamide (**193**)

[0796] Following the same procedure as described in Example 14, step 4 (scheme 14) but substituting compound **146** for compound **192**, the title compound **193** was obtained after column chromatography (46% yield, eluent: 50% MeOH in DCM with 1% triethylamine).



[0797]  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  (ppm): 9.58 (s, 1H), 7.97 (d,  $J$ = 9.0 Hz, 2H), 7.40 (d,  $J$ = 1.8 Hz, 1H), 7.23 to 7.21 (m, 1H), 7.05 to 7.02 (m, 3H), 6.86 (d,  $J$ = 3.5 Hz, 1H), 6.77 (d,  $J$ = 8.4 Hz, 1H), 5.10 (s, 2H), 4.53 (m, 1H), 3.88 (s, 2H), 3.83 (s, 3H), 3.47 (q,  $J$ = 5.5 Hz, 2H), 2.63 (t,  $J$ = 5.5 Hz, 2H). LRMS: 397.4 (calc) 795.5 (obs for  $2\text{M}+\text{H}$ ).

Table 12: Characterization of compound **194** prepared according to Scheme 20



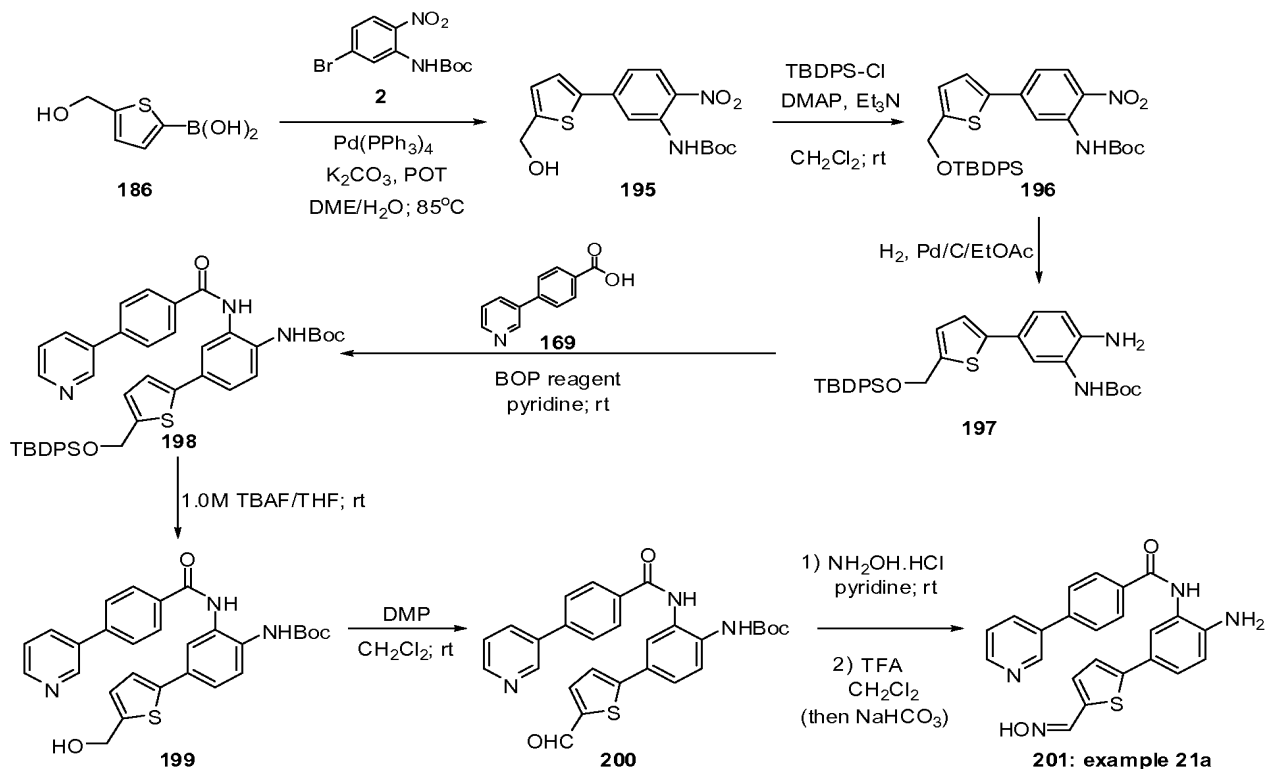
**194**

Cpd	Ex	Name	Characterization
<b>194</b>	<b>20b</b>	N-(5-(5-((1H-pyrazol-5-ylamino)methyl)thiophen-2-yl)-2-aminophenyl)-4-methoxybenzamide	$^1\text{H}$ NMR ( $\text{DMSO-d}_6$ ) $\delta$ (ppm): 11.52 (s, 1H), 9.58 (s, 1H), 7.96 (d, $J$ = 8.8 Hz, 2H), 7.37 (d, $J$ = 2.2 Hz, 1H), 7.32 (m, 1H), 7.19 (dd, $J$ = 8.2, 2.2 Hz, 1H), 7.04 to 7.01 (m, 3H), 6.87 (d, $J$ = 3.5 Hz, 1H), 6.76 (d, $J$ = 8.2 Hz, 1H), 5.64 (bs, 1H), 5.47 (s, 1H), 5.08 (s, 2H), 4.33 (d, $J$ = 6.3 Hz, 2H), 3.83 (s, 3H). LRMS: 419.50 (calc) 420.2 (obs).

#### Example 21a

*N*-(2-Amino-5-(5-((hydroxyimino)methyl)thiophen-2-yl)phenyl)-4-(pyridin-3-yl)benzamide  
(201)

## Scheme 21

Step 1: tert-Butyl 5-(5-(hydroxymethyl)thiophen-2-yl)-2-nitrophenylcarbamate (195)

[0798] Following the same procedure as described in Example 1, step 2 (scheme 1), but substituting 2-thiophene boronic acid for compound 186, title compound 195 was obtained in 48% yield [after flash chromatography (eluent: 20 to 50% AcOEt in hexane)].

[0799]  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  (ppm): 9.62 (s, 1H), 8.08 (d,  $J = 2.2$  Hz, 1H), 7.87 (dd,  $J = 8.6$ , 2.3 Hz, 1H), 7.64 (d,  $J = 8.6$  Hz, 1H), 6.96 (d,  $J = 3.5$  Hz, 1H), 5.57 (t,  $J = 5.7$  Hz, 1H), 4.63 (d,  $J = 5.7$  Hz, 2H), 1.45 (s, 9H). LRMS: 350.09 (calc) 373.1 (obs  $\text{M}+\text{Na}$ ).

Step 2: tert-Butyl 5-(5-((tert-butyl-diphenylsilyloxy)methyl)thiophen-2-yl)-2-nitrophenylcarbamate (196)

[0800] Following the same procedure as described in Example 20, step 3 (scheme 20), but substituting compound 187 for compound 195, diisopropylethyl amine for triethylamine, and pyridine for DCM, title compound 196 was obtained after column chromatography (94% yield, eluent: 50% DCM in hexane).

[0801] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.64 (s, 1H), 8.09 (d, J= 2.3 Hz, 1H), 7.89 (dd, J= 8.4, 2.2 Hz, 1H), 7.66 to 7.63 (m, 5H), 7.49 to 7.42 (m, 7H), 6.94 (d, J= 3.7 Hz, 1H), 4.91 (s, 2H), 1.46 (s, 9H), 1.04 (s, 9H). LRMS: 588.21 (calc) 587.3 (obs M-H).

Step 3: *tert*-Butyl 2-amino-5-(5-((*tert*-butyldiphenylsilyloxy)methyl)thiophen-2-yl)phenylcarbamate (197)

[0802] Following the same procedure as described in Example 1, step 3 (scheme 1), but substituting compound 3 for compound 196, title compound 197 was obtained (98% yield).

[0803] LRMS: 502.17 (calc M-*t*Bu) 503.4 (obs M-*t*Bu).

Step 4: *tert*-Butyl 4-(5-((*tert*-butyldiphenylsilyloxy)methyl)thiophen-2-yl)-2-(4-(pyridin-3-yl)benzamido)phenylcarbamate (198)

[0804] Following the same procedure as outlined in Example 1, step 6 (scheme 1), but substituting compound 7 for compound 169 and compound 4 for compound 197, and using a catalytic amount of 4-dimethylaminopyridine, title compound 198 was obtained in 76% yield [after column chromatography (eluent: 50% AcOEt in hexane)].

[0805] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 10.01 (s, 1H), 8.99 (d, J= 2.3 Hz, 1H), 8.73 (s, 1H), 8.61 (dd, J= 4.9, 1.6 Hz, 1H), 8.19-8.16 (m, 1H), 8.10 (d, J= 8.4 Hz, 2H), 7.94 (d, J= 8.4 Hz, 2H), 7.78 (d, J= 2.2 Hz, 1H), 7.66-7.62 (m, 5H), 7.54-7.41 (m, 8H), 7.29 (d, J= 3.7 Hz, 1H), 6.91 (d, J= 3.5 Hz, 1H), 4.90 (s, 2H), 1.47 (s, 9H), 1.04 (s, 9H). LRMS: 739.29 (calc) 740.3 (obs).

Step 5: *tert*-Butyl 4-(5-(hydroxymethyl)thiophen-2-yl)-2-(4-(pyridin-3-yl)benzamido)-phenylcarbamate (199)

[0806] Following the same procedure as described in Example 20, step 5 (scheme 20) but substituting compound 189 for compound 198, title compound 199 was obtained in 90% yield [after column chromatography (eluent: 25% AcOEt in DCM)].

[0807] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.97 (s, 1H), 8.99 (d, J= 2.3 Hz, 1H), 8.75 (s, 1H), 8.61 (dd, J= 4.7, 1.6 Hz, 1H), 8.18 (dq, J= 7.8, 1.6 Hz, 1H), 8.10 (d, J= 8.4 Hz, 2H), 7.93 (d, J= 8.2 Hz, 2H), 7.79 (d, J= 2.2 Hz, 1H), 7.60 (d, J= 8.4 Hz, 1H), 7.54 to 7.51 (m, 1H), 7.47 (dd, J= 8.4, 2.2 Hz, 1H), 7.28 (d, J= 3.5 Hz, 1H), 6.93 (d, J= 3.5 Hz, 1H), 5.51 (t, J= 5.9 Hz, 1H), 4.62 (d, J= 5.7 Hz, 2H), 1.47 (s, 9H). LRMS: 501.17 (calc) 502.1 (obs).

Step 6: *tert*-Butyl 4-(5-formylthiophen-2-yl)-2-(4-(pyridin-3-yl)benzamido)phenylcarbamate (200)

[0808] Following the same procedure as described in Example 20, step 6 (scheme 20), but substituting compound **190** for compound 199, title compound 200 was obtained in 24% yield [after column chromatography (eluent: 5% isopropanol in DCM)].

[0809] LRMS: 499.2 (calc) 500.1 (obs).

Steps 7 & 8: *N*-(2-Amino-5-(5-((hydroxyimino)methyl)thiophen-2-yl)phenyl)-4-(pyridin-3-yl)benzamide (201)

[0810] A solution of aldehyde 200 (20.4 mgs, 0.41 mmol) in pyridine (4 mL) was treated with solid hydroxylamine hydrochloride (0.344 g, 4.95 mmol) and the solution was stirred at room temperature for 4 h, diluted with DCM, washed with saturated NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatotron (eluent: 5% MeOH in DCM) to provide a solid material (25 mg, structure not shown in the scheme 21). LRMS: 514.2 (calc) 515.2 (obs).

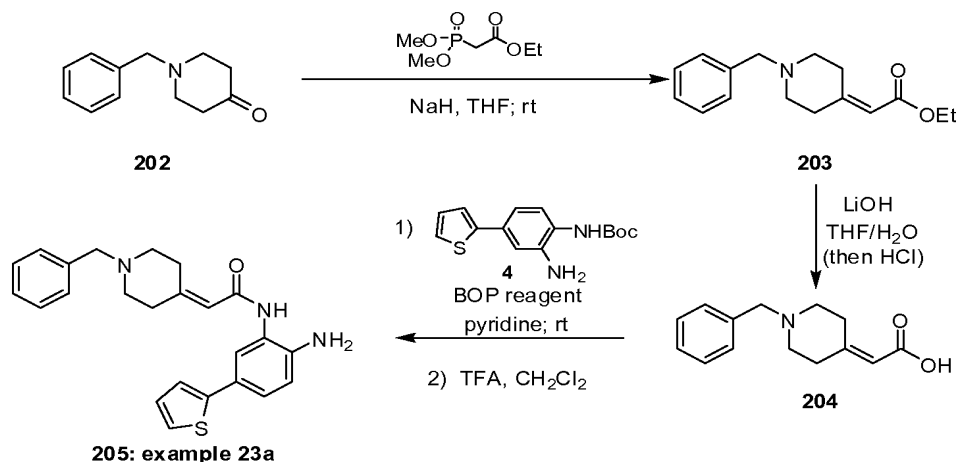
[0811] Following the same procedure as described in Example 1, step 7 (scheme 1), but substituting compound 8 for the above mentioned material, the title compound 201 was obtained in 62% yield [after column chromatography (eluent: 10% isopropanol in DCM)].

[0812] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 11.77 (s, 1H), 9.80 (s, 1H), 8.98 (d, *J* = 1.8 Hz, 1H), 8.61 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.18 to 8.16 (m, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.74 (s, 1H), 7.56 to 7.51 (m, 2H), 7.36 (q, *J* = 3.9 Hz, 2H), 7.26 (d, *J* = 3.9 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.31 (s, 2H). LRMS: 414.1 (calc), 414.9 (obs).

**Example 22a**

***N*-(2-Amino-5-(thiophen-2-yl)phenyl)-2-(1-benzylpiperidin-4-ylidene)acetamide (205)**

Scheme 22



#### Step 1: Ethyl 2-(1-benzylpiperidin-4-ylidene)acetate (**203**)

[0813] To a suspension of sodium hydride (4.8 g, 121 mmol) in THF (300 mL) was added a solution of ethyl 2-(dimethoxyphosphoryl)acetate (24.3 mL, 121.2 mmol) in THF (60 mL) drop wise over 30 min. After complete addition the solution was stirred for 10 min then a solution of ketone 202 (15.3 g, 80.8 mmol) in THF (80 mL) was added drop wise over 20 min. After 60 min of stirring at room temperature, the reaction mixture was quenched with H<sub>2</sub>O, extracted with diethyl ether. The organic phase were washed with H<sub>2</sub>O, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and purified by column chromatography (30 to 40% AcOEt in hexane) to give title compound 203 (20.4 g, 98% yield).

[0814] LRMS: 259.20 (calc) 260.1 (obs).

#### Step 2: 2-(1-Benzylpiperidin-4-ylidene)acetic acid (**204**)

[0815] To a solution of ester **203** (8.06 g, 31.1 mmol) in THF (100 mL) was added an aqueous solution of LiOH (1.96 g, 46.6 mmol) in water (30 mL) and the reaction mixture was allowed to stir at 45 °C for 60 min. Then more LiOH (0.5 g, 11.9 mmol) was added to the heating solution. After further heating for 8 h, the reaction mixture was concentrated, extracted with AcOEt. The extract was concentrated and the residue was combined with the white solid which was collected by filtration from the aqueous phase. The combined solid materials were dissolved in DCM, treated with 2N HCl in diethyl ether (10 mL) and the mixture was diluted with benzene, evaporated and dried under vacuum to give (presumably) mono-hydrochloride salt of the acid **204** (8.23 g, 99% yield).

[0816]  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  (ppm): 7.58 to 7.54 (m, 2H), 7.51 to 7.48 (m, 3H), 5.86 (s, 1H), 4.36 (s, 2H), 3.35 to 3.13 (m, 6H), 2.66 to 2.63 (m, 2H). LRMS: 231.13 (calc) 232.1 (obs).

Steps 3 & 4: *N*-(2-Amino-5-(thiophen-2-yl)phenyl)-2-(1-benzylpiperidin-4-ylidene)acetamide (205)

[0817] Following the same procedure as described in Example 1, steps 6 & 7 (scheme 1), but substituting compound 7 for compound 204, the title compound 205 was obtained (step 3: 34% yield, step 4: 33% yield).

[0818]  $^1\text{H}$  NMR ( $\text{MeOH}-d_4$ )  $\delta$  (ppm): 7.44 (d,  $J = 2.0\text{Hz}$ , 1H), 7.36-7.27 (m, 6H), 7.22 (dd,  $J = 5.2, 0.8\text{Hz}$ , 1H), 7.19 (dd,  $J = 3.6, 1.2\text{Hz}$ , 1H), 7.01 (dd,  $J = 5.2, 3.6\text{Hz}$ , 1H), 6.85 (d,  $J = 8.4\text{Hz}$ , 1H), 5.94 (s, 1H), 3.57 (s, 2H), 3.06 (t,  $J = 6.0\text{Hz}$ , 2H), 2.61-2.54 (m, 4H), 2.40 (t,  $J = 5.6\text{Hz}$ , 2H) LRMS: 403.5 (calc) 404.2 (obs).

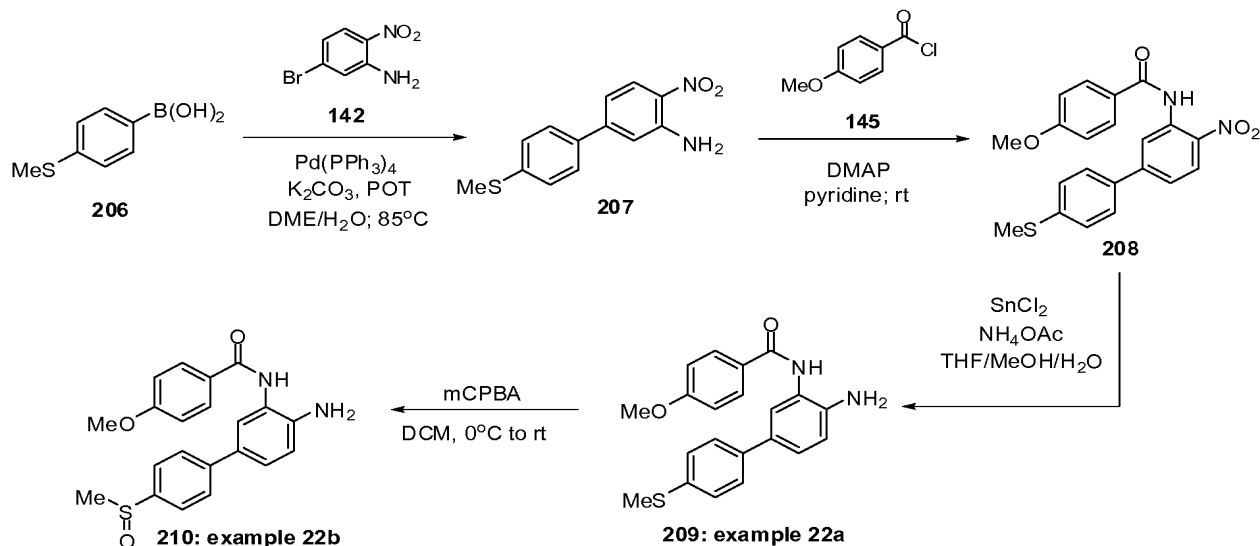
### Example 23a

***N*-(4-Amino-4'-(methylthio)biphenyl-3-yl)-4-methoxybenzamide (209)**

**and Example 23b**

***N*-(4-Amino-4'-(methylsulfinyl)biphenyl-3-yl)-4-methoxybenzamide (210)**

### Scheme 23



Step 1: 4'-(Methylthio)-4-nitrobiphenyl-3-amine (207)

[0819] Following the same procedure as described in Example 1, step 2 (scheme 1), but substituting 2-thiophene boronic acid for compound 206, and compound 2 for compound 142,

title compound 207 was obtained in 100% yield [after column chromatography (eluent: 20 to 50% AcOEt in hexane)].

[0820] <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ (ppm): 8.01 (d, J= 9.0 Hz, 1H), 7.59 (dd, J= 6.7, 2.0 Hz, 2H), 7.45 (s, 2H), 7.36 (dd, J= 6.7, 2.0 Hz, 2H), 7.26 (d, J= 2.0 Hz, 1H), 6.91 (dd, J= 9.0, 2.0 Hz, 1H), 2.52 (s, 3H).

Step 2: 4-Methoxy-N-(4'-(methylthio)-4-nitrobiphenyl-3-yl)benzamide (208)

[0821] Following the same procedure as described in Example 14, step 3 (scheme 14), but substituting compound 144 for compound 207, title compound 208 was obtained (66% yield).

[0822] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 10.70 (s, 1H), 8.17 (d, J= 2.0 Hz, 1H), 8.08 (d, J= 8.4 Hz, 1H), 7.95 (dd, J= 6.8, 1.8 Hz, 2H), 7.71 (dd, J= 8.8, 2.3 Hz, 2H), 7.66 (dd, J= 8.4 Hz, 1H), 7.40 (d, J= 8.2 Hz, 2H), 7.11 (d, J= 8.8 Hz, 2H), 3.86 (s, 3H), 2.54 (s, 3H).

Step 3: 4-Methoxy-N-(4'-(methylthio)-4-nitrobiphenyl-3-yl)benzamide (209)

[0823] Following the same procedure as described in Example 14, step 4 (scheme 14), but substituting compound 146 for compound 208, title compound 209 was obtained in 54% yield [after column chromatography (eluent: 5% isopropanol in DCM) and trituration from pentane/diethyl ether].

[0824] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.63 (s, 1H), 7.99 (d, J= 8.8 Hz, 2H), 7.52 to 7.48 (m, 3H), 7.32 to 7.27 (m, 3H), 7.06 (d, J= 8.8 Hz, 2H), 6.85 (d, J= 8.4 Hz, 1H), 5.07 (s, 2H), 3.84 (s, 3H), 2.49 (s, 3H). LRMS: 364.1 (calc), 365.1 (obs).

Step 4: N-(4-amino-4'-(methylsulfinyl)biphenyl-3-yl)-4-methoxybenzamide (210)

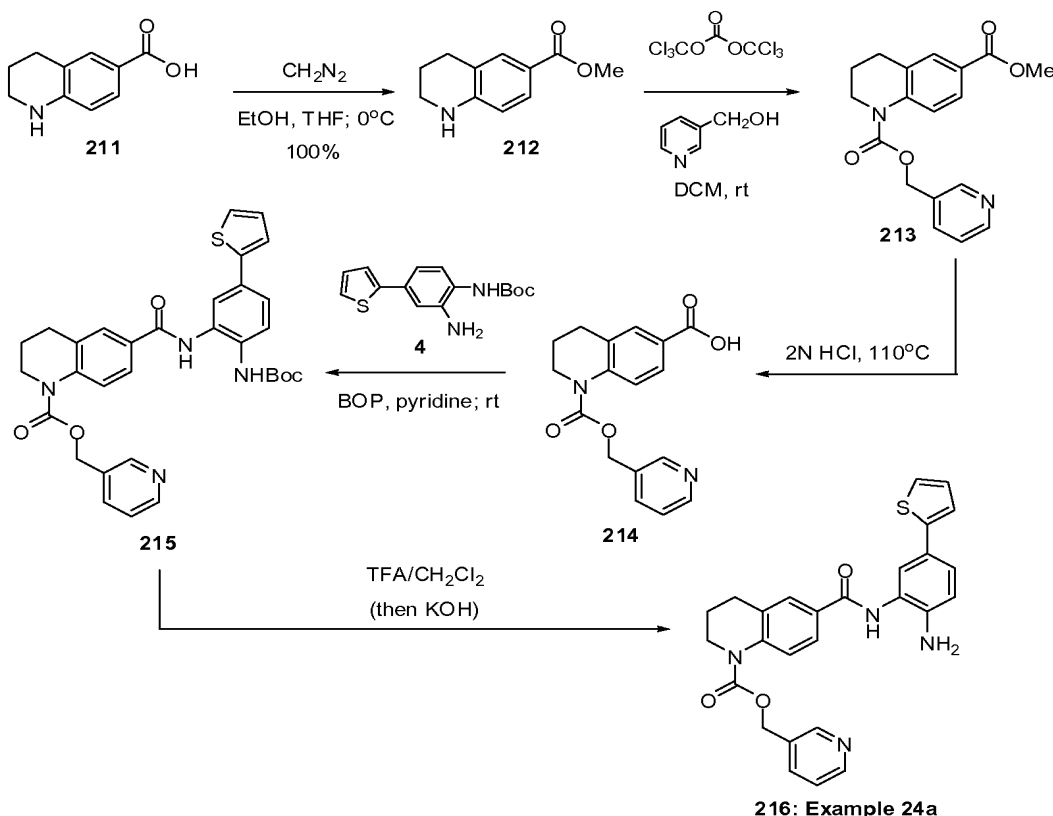
[0825] Following the same procedure as described in Example 10, step 2 (scheme 10), but substituting compound 120 for compound 209, the title compound 210 was obtained in 57% yield [after column chromatography (5% isopropanol in DCM)].

[0826] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.64 (s, 1H), 8.00 (d, J= 9.0 Hz, 2H), 7.76 (d, J= 7.69 (d, J= 8.6 Hz, 2H), 7.58 (d, J= 2.2 Hz, 1H), 7.40 (dd, J= 8.4 Hz, 1H), 7.06 (d, J= 9.0 Hz, 2H), 6.88 (d, J= 8.4 Hz, 1H), 5.21 (s, 2H), 3.84 (s, 3H), 2.76 (s, 3H). LRMS: 380.1 (calc), 380.9 (obs).

## Example 24a

Pyridin-3-ylmethyl 6-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**216**)

## Scheme 24

**216: Example 24a**Step 1: Methyl 1,2,3,4-tetrahydroquinoline-6-carboxylate (**212**)

**[0827]** A mixture of 50% potassium hydroxide in  $\text{H}_2\text{O}$  (30 mL) and diethyl ether (100 mL), stirred at  $0^\circ\text{C}$ , was treated portion-wise with solid *N*-nitroso-*N*-methyl urea (3.0g, 29.1 mmol). The reaction mixture was stirred for 30 min then transferred into a separatory funnel, the aqueous layer was discarded and the yellow ethereal phase (diazomethane solution) was cooled to  $-78^\circ\text{C}$  in an Erlenmeyer flask. To a solution of acid **211** (1.0g, 5.65 mmol) in THF (100 mL), stirred at  $0^\circ\text{C}$ , was added the ethereal solution of diazomethane (kept at  $-78^\circ\text{C}$ ) drop wise. After the addition, the reaction mixture was stirred at  $0^\circ\text{C}$  for 2 h then at room temperature for 4 h, and concentrated to give title compound **212** as a reddish solid (100% yield).

**[0828]**  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  (ppm): 7.47 to 7.45 (m, 2H), 6.63 (s, 1H), 6.42 (d,  $J = 8.4$  Hz, 1H), 3.71 (s, 3H), 3.24-3.21 (m, 2H), 2.67 (t,  $J = 6.3$  Hz, 2H), 1.80-1.74 (m, 2H).



Step 2: 6-Methyl 1-pyridin-3-ylmethyl 3,4-dihydroquinoline-1,6(2H)-dicarboxylate (**213**)

[0829] A solution of triphosgene (0.489g, 1.61 mmol) in DCM (5 mL) was treated with compound **212** (0.286 g, 1.50 mmol) and the solution was stirred under N<sub>2</sub> atmosphere at room temperature for 18 h. The DCM was removed under reduced pressure, the residue was dissolved in pyridin-3-yl methanol (1.0 mL, 10.3 mmol) and the solution was stirred at room temperature for 8 h then diluted with DCM, washed with saturated NaHCO<sub>3</sub>, H<sub>2</sub>O, dried over MgSO<sub>4</sub>, filtered and concentrated to give title compound **213** (0.527g, 100% yield).

[0830] LRMS: 326.1 (calc) 327.1 (obs)

Step 3: 1-((Pyridin-3-ylmethoxy)carbonyl)-1,2,3,4-tetrahydroquinoline-6-carboxylic acid (**214**)

[0831] A solution of ester **213** (0.489 g, 1.50 mmol) in 2N HCl (10 mL) was stirred at 110 °C for 3 h then concentrated, suspended in dry acetonitrile (20 mL), stirred for 2 h, diluted with dry benzene (20 mL), and stirred for 6 h. The suspension was concentrated then re-suspended in 1:1 acetonitrile and benzene (20 mL). The solid material was collected by filtration to provide title compound **214** (0.460 g, 88% yield).

[0100] LRMS: 312.1 (calc) 313.1 (obs)

Step 4: Pyridin-3-ylmethyl 6-(2-(tert-butoxycarbonylamino)-5-(thiophen-2-yl)phenylcarbamoyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**215**)

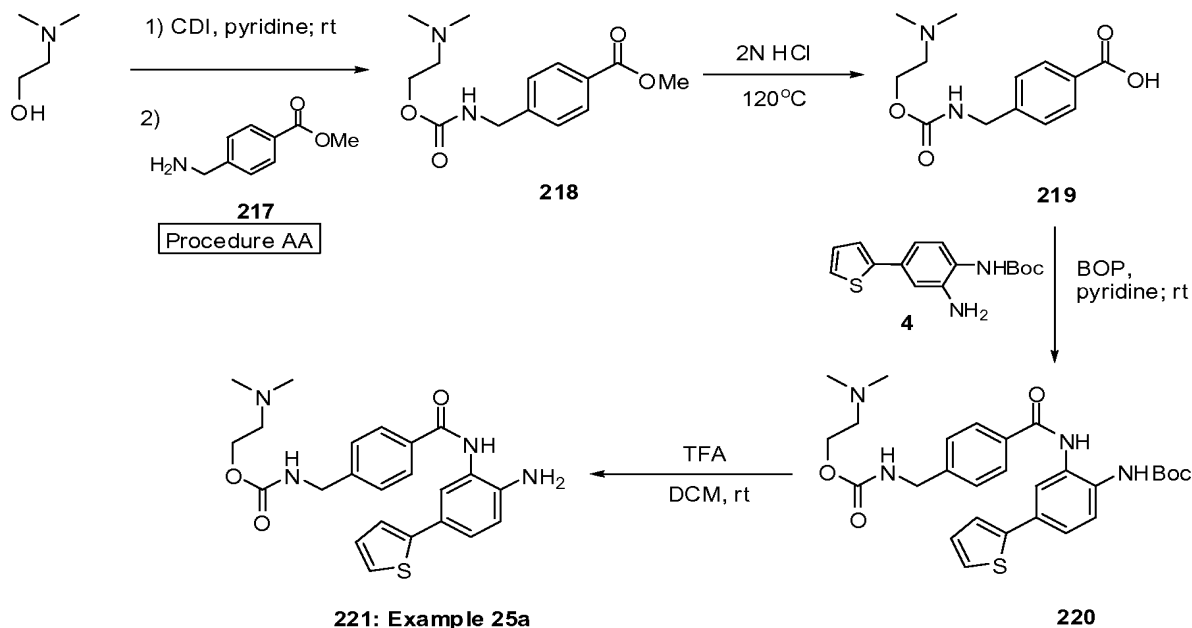
[0832] Following the same procedure as described in Example 1, step 6 (example 1), but substituting compound **7** for compound **214**, title compound **215** was obtained in 55% yield [after flash chromatography (eluent: 50% AcOEt in DCM)].

[0833] LRMS: 584.2 (calc) 484.16 (M-tBoc, obs)

Step 5: Pyridin-3-ylmethyl 6-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)-3,4-dihydroquinoline-1(2H)-carboxylate (**216**)

[0834] Following the same procedure as described in Example 1, step 7 (scheme 1), but substituting compound **8** for compound **215**, and NaHCO<sub>3</sub> for KOH, the title compound **216** was obtained in 89% yield.

[0835] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.67 (s, 1H), 8.67 (d, J= 1.6 Hz, 1H), 8.56 (dd, J= 4.9, 1.8 Hz, 1H), 7.89 to 7.86 (m, 1H), 7.82 to 7.79 (m, 3H), 7.46 to 7.43 (m, 2H), 7.36 (dd, J= 5.1, 1.2 Hz, 1H), 7.29 (dd, J= 3.5, 2.2 Hz, 1H), 7.24 (dd, J= 3.5, 1.2 Hz, 1H), 7.05 (dd, J= 5.1, 3.5 Hz, 1H), 6.81 (d, J= 8.4 Hz, 1H), 5.27 (s, 2H), 5.14 (s, 2H), 3.78 (t, J= 6.1 Hz, 2H), 2.81 (t, J= 6.4 Hz, 2H), 1.91 to 1.88 (m, 2H). LRMS: 484.16 (calc) 485.2 (obs).

**Example 25a****2-((Dimethylamino)ethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)benzylcarbamate (221))****Scheme 25****Step 1: Methyl 4-(((2-(dimethylamino)ethoxy)carbamoyl)amino)methyl)benzoate (218)**

**[0836]** A solution of carbonyl diimidazole (CDI) (609 mg, 3.76 mmol) in pyridine (5 mL) was treated with neat dimethylaminoethanol (400  $\mu$ L, 3.98 mmol) and the mixture was stirred for 15 h at room temperature. Methyl 4-(aminomethyl)benzoate hydrochloride (217) (794 mg, 3.82 mmol) was then added and the reaction mixture was stirred for further 7 h, diluted with DCM, washed with saturated NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered and concentrated to produce title compound 218 as a white solid (1.16 g, >100% yield, crude, used without additional purification).

**[0837]** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  (ppm): 7.93 to 7.90 (m, 2H), 7.38 (d, J= 8.2 Hz, 2H), 4.25 (d, J= 6.1 Hz, 2H), 4.04 (t, J= 5.9 Hz, 2H), 3.84 (s, 3H), 2.43 (t, J= 5.9 Hz, 2H), 2.15 (s, 6H).

**Step 2: 4-(((2-(Dimethylamino)ethoxy)carbamoyl)amino)methyl)benzoic acid (219)**

**[0838]** Following the same procedure as described in Example 1, step 5 (scheme 1), but substituting compound 6 for compound 218, title compound 219 was obtained in 100% yield.

**[0839]** LRMS: 266.1 (calc) 267.1 (obs)

Step 3: 2-(Dimethylamino)ethyl 4-(2-*tert*-butoxycarbonyl-amino-5-(thiophen-2-yl)phenylcarbamoyl)benzylcarbamate (220)

[0840] Following the same procedure as described in Example 1, step 6 (scheme 1), but substituting compound 7 for compound 219, title compound 220 was obtained (40% yield).

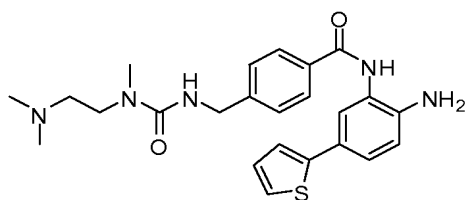
[0841] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 9.89 (s, 1H), 8.74 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 2.2 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.54 to 7.50 (m, 2H), 7.46 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.13 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.27 (d, *J* = 6.1 Hz, 2H), 4.07 (t, *J* = 5.9 Hz, 2H), 2.48 to 2.47 (m, 2H), 2.19 (s, 6H), 1.46 (s, 9H).

Step 4: 2-(Dimethylamino)ethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)benzylcarbamate (221)

[0842] Following the same procedure as described in Example 1, step 7 (scheme 1), but substituting compound 8 for compound 220, the title compound 221 was obtained in 78% yield.

[0843] <sup>1</sup>H NMR: (DMSO-*d*<sub>6</sub>) δ (ppm): 9.71 (s, 1H), 7.96 (d, *J* = 9.0 Hz, 2H), 7.82 (t, *J* = 6.1 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.39 (s, 1H), 7.36 (d, *J* = 1.2 Hz, 1H), 7.35 (d, *J* = 1.2 Hz, 1H), 7.30 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.25 (dd, *J* = 3.5, 1.2 Hz, 1H), 7.05 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.16 (s, 2H), 4.25 (d, *J* = 6.1 Hz, 2H), 4.06 (t, *J* = 5.8 Hz, 2H), 2.45 (t, *J* = 5.8 Hz, 2H), 2.17 (s, 6H). LRMS: 438.2 (calc) 439.1 (obs)

Table 13: Characterization of compound 222 prepared according to Scheme 25

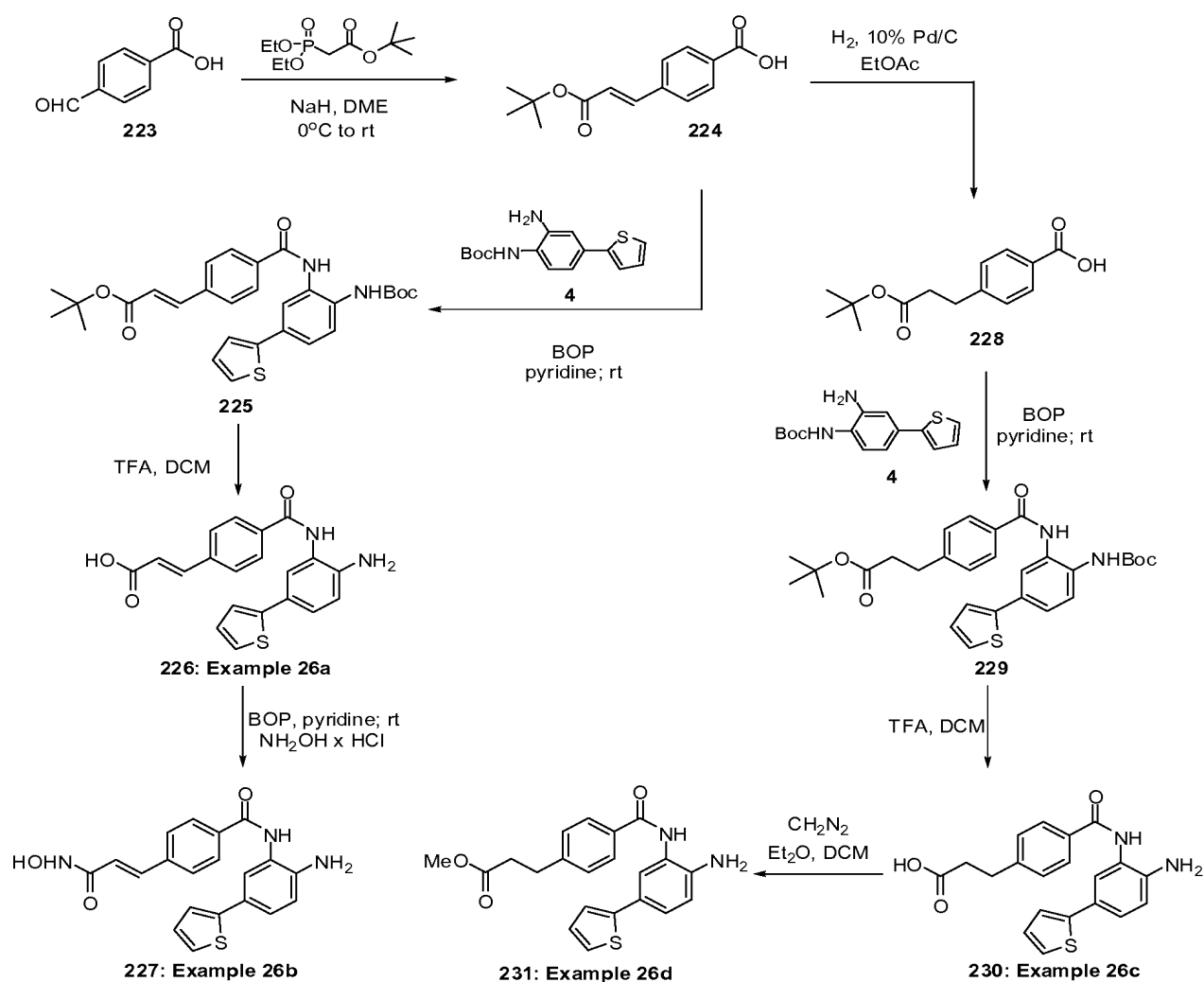


**222: Example 25b**

Cpd	Ex	Name	Characterization
222	25b	N-(2-amino-5-(thiophen-2-yl)phenyl)-4-((3-(2-(dimethylamino)ethyl)-3-methylureido)methyl)benzamide	<sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ) δ (ppm): 9.70 (s, 1H), 7.94 (d, <i>J</i> = 8.2 Hz, 2H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.39 to 7.35 (m, 3H), 7.30 (dd, <i>J</i> = 8.2, 2.2 Hz, 1H), 7.25 (dd, <i>J</i> = 3.5, 0.98 Hz, 1H), 7.05 (dd, <i>J</i> = 5.1, 3.5 Hz, 2H), 6.81 (d, <i>J</i> = 8.4 Hz, 1H), 5.76 (s, 2H), 4.30 (d, <i>J</i> = 5.9 Hz, 2H), 3.31 (t, <i>J</i> = 6.7 Hz, 2H), 2.85 (s, 3H), 2.36 (t, <i>J</i> = 6.7 Hz, 2H), 2.18 (s, 6H). LRMS: 451.2 (calc) 452.3 (obs)

**Example 26a**

**(E)-3-(4-(2-Amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl)acrylic acid (226)**

**Example 26b****(E)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(3-(hydroxyamino)-3-oxoprop-1-enyl)benzamide (227)****Example 26c****3-(4-(2-Amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl)propanoic acid (230)****Example 26d****Methyl 3-(4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl)propanoate (231)****Scheme 26**

Step 1: (E)-4-(3-*tert*-Butoxy-3-oxoprop-1-enyl)benzoic acid (224)

[0844] A solution of 4-formylbenzoic acid (**223**) (306 mg, 2.04 mmol) and *tert*-butyl 2-(diethoxyphosphoryl)acetate (0.8 mL, 3.23 mmol) in ethyleneglycol dimethylether (15 mL) was stirred at 0 °C then treated with sodium hydride (60% in oil, 312 mg, 7.8 mmol), further stirred for 1 h then at room temperature for 3 h. The reaction mixture was diluted with acetone, stirred 10 min then treated with 5% aqueous KHSO<sub>4</sub>, extracted with DCM. The extract was dried over MgSO<sub>4</sub>, filtered and concentrated to provide title compound **224** as a white solid (811.5 mg, >100% yield, crude, used in the next step without additional purification).

[0845] LRMS: 248.10 (calc) 247.0 (M-H)

Step 2: (E)-*tert*-Butyl 3-(4-(2-(*tert*-butoxycarbonylamino)-5-(thiophen-2-yl)phenylcarbamoyl)phenyl)acrylate (225)

[0846] Following the procedure as described in Example 1, step 6 (scheme 1), but substituting compound **7** for compound **224**, title compound **225** was obtained in 42% yield (over 2 steps starting from the acid **223**).

[0847] LRMS: 520.20 (calc) 543.1 (M+Na)

Step 3: (E)-3-(4-(2-Amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl)acrylic acid trifluoroacetate (1:1) (226)

[0848] Following the same procedure as described in Example 1, step 7 (scheme 1), but substituting compound **8** for compound **225**, the title compound **226** was obtained as a white solid in quantitative yield.

[0849] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 9.96 (s, 1H), 8.04 (d, J= 8.4 Hz, 2H), 7.86 (d, J= 8.6 Hz, 2H), 7.67 (d, J= 16.0 Hz, 1H), 7.52 (d, J= 1.8 Hz, 1H), 7.41 (dd, J= 4.7, 0.98 Hz, 1H), 7.38 (dd, J= 8.0, 2.0 Hz, 1H), 7.31 (d, J= 2.5 Hz, 1H), 7.07 (dd, J= 5.1, 3.5 Hz, 1H), 6.93 (d, J= 8.0 Hz, 1H), 6.68 (d, J= 16.0 Hz, 1H). LRMS: 364.1 (calc) 364.9 (obs)

Step 4: (E)-*N*-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(3-(hydroxyamino)-3-oxoprop-1-enyl)benzamide (227)

[0850] Following the same procedure as described in Example 1, step 6 (scheme 1), but substituting compound **4** for *N*-hydroxylamine hydrochloride salt and compound **7** for compound **226**, the title compound **227** was obtained as a yellowish solid in 79% yield [purified by flash chromatography (eluent: 5% to 66% MeOH in DCM)].

[0851] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.81 (s, 1H), 8.04 (d, J= 8.0 Hz, 2H), 7.69 (d, J= 7.6 Hz, 2H), 7.47 (d, J= 2.0 Hz, 2H), 7.36 (dd, J= 4.9, 0.78 Hz, 1H), 7.30 (dd, J= 8.2, 2.3 Hz, 1H), 7.25 (dd, J= 3.5, 0.78 Hz, 1H), 7.05 (dd, J= 5.1, 3.7 Hz, 1H), 6.81 (d, J= 8.4 Hz, 1H), 6.61 (d, J= 16.4 Hz, 1H), 5.19 (s, 2H). LRMS: 379.0 (calc) 380.0 (obs).

Step 5: 4-(3-*tert*-Butoxy-3-oxopropyl)benzoic acid (228)

[0852] Following the same procedure as described in Example 1, step 3 (scheme 1), but substituting compound 3 for compound 224, title compound 228 was obtained in quantitative yield.

[0853] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 7.85 (d, J= 8.0 Hz, 2H), 7.34 (d, J= 8.4 Hz, 2H), 2.87 (t, J= 7.6 Hz, 2H), 2.46 (t, J= 7.6 Hz, 2H), 1.34 (s, 9H).

Step 6: *tert*-Butyl 3-(4-(2-(*tert*-butoxycarbonylamino)-5-(thiophen-2-yl)phenylcarbamoyl)phenyl)propanoate (229)

[0854] Following the same procedure as described in Example 1, step 6 (scheme 1), but substituting compound 7 for compound 228, intermediate 229 was obtained (88% yield).

[0855] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.87 (s, 1H), 8.76 (s, 1H), 7.90 (d, J= 8.2 Hz, 2H), 7.82 (d, J= 2.2 Hz, 1H), 7.60 (d, J= 8.6 Hz, 1H), 7.54 to 7.50 (m, 2H), 7.46 (dd, J= 3.7, 1.2 Hz, 1H), 7.41 (d, J= 8.4 Hz, 2H), 7.13 (dd, J= 5.1, 3.7 Hz, 1H), 2.90 (t, J= 7.2 Hz, 2H), 2.58 (t, J= 7.2 Hz, 2H), 1.45 (s, 9H), 1.37 (s, 9H).

Step 7: 3-(4-(2-Amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl)propanoic acid (230)

[0856] Following the same procedure as described in Example 1, Step 7 (scheme 1), but substituting compound 8 for intermediate 229, the title compound 230 was obtained as its trifluoroacetic acid salt (88% yield).

[0857] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.68 (s, 1H), 7.92 (d, J= 8.2 Hz, 2H), 7.47 (d, J= 2.2 Hz, 1H), 7.39 to 7.35 (m, 3H), 7.29 (dd, J= 8.4, 2.3 Hz, 1H), 7.24 (dd, J= 3.5, 1.2 Hz, 1H), 7.05 (dd, J= 5.1, 3.5 Hz, 1H), 6.81 (d, J= 8.4 Hz, 1H), 5.15 (s, 2H), 2.90 (t, J= 7.6 Hz, 2H), 2.58 (t, J= 7.4 Hz, 2H).

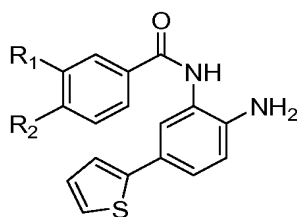
Step 8: Methyl 3-(4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl)propanoate (231)

[0858] A mixture of 50% potassium hydroxide in H<sub>2</sub>O (30 mL) and diethyl ether (100 mL), stirred at 0 °C, was treated portion wise with solid *N*-nitroso-*N*-methyl urea (3.0 g, 29.1 mmol). The reaction mixture was stirred for 30 min then transferred into a separatory funnel, the aqueous layer was discarded and the yellow ethereal phase (diazomethane solution) was cooled to -78 °C

in an Erlenmeyer flask. A suspension of the acid **230** (20 mg, 0.055 mmol) in DCM (2 mL) was treated with the diazomethane solution in diethyl ether (3 mL) and the yellow solution was stirred at room temperature for 3 h, concentrated and the residue was purified by flash chromatography (eluent: 2% isopropanol in DCM) to provide title compound **231** (19.7 mg, 94% yield).

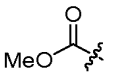
[0859]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 9.69 (s, 1H), 7.92 (d,  $J$ = 8.2 Hz, 2H), 7.46 (d,  $J$ = 2.0 Hz, 1H), 7.38 to 7.35 (m, 3H), 7.30 (dd,  $J$ = 8.2, 2.2 Hz, 1H), 7.24 (dd,  $J$ = 3.5, 1.2 Hz, 1H), 7.05 (dd,  $J$ = 5.1, 3.5 Hz, 1H), 6.81 (d,  $J$ = 8.4 Hz, 1H), 5.16 (s, 2H), 3.59 (s, 3H), 2.93 (t,  $J$ = 7.4 Hz, 2H), 2.69 (t,  $J$ = 7.4 Hz, 2H). LRMS: 380.12 (calc) 381.2 (obs).

Table 14: Characterization of compounds **232-235** prepared according to Scheme 26



**232-235**

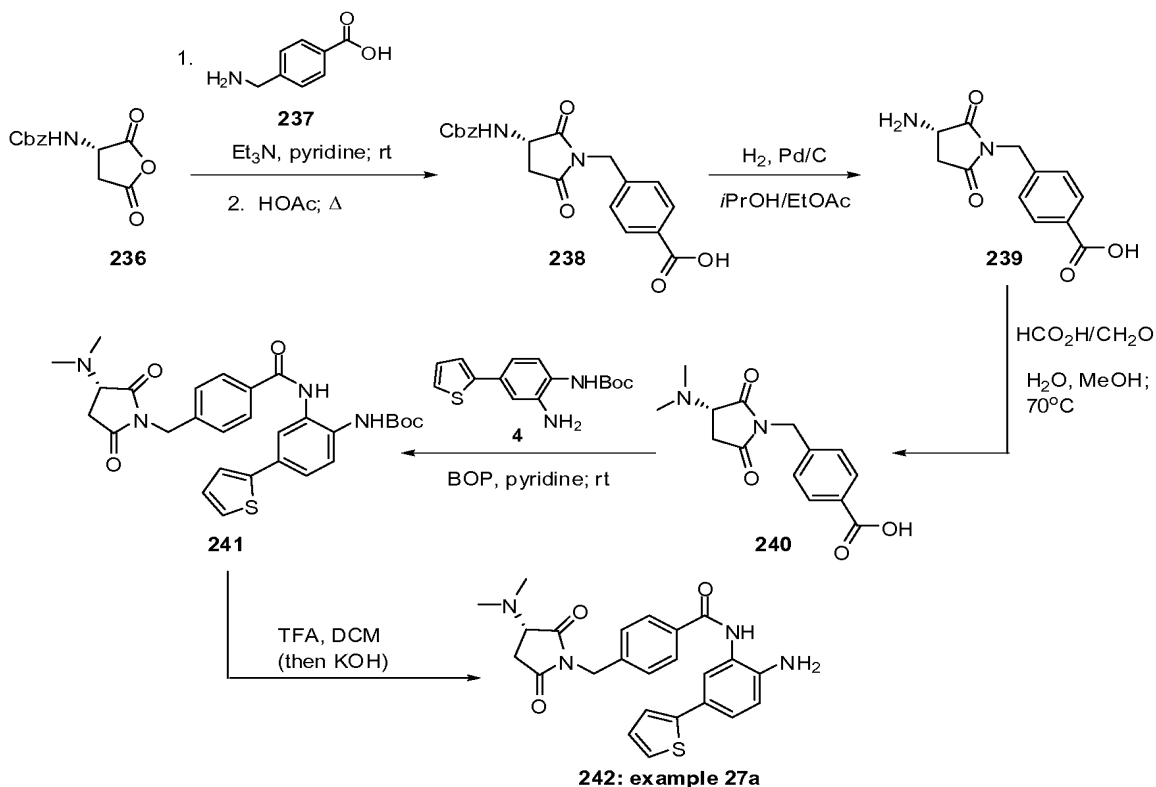
Cpd	Ex	R <sub>1</sub>	R <sub>2</sub>	Name	Characterization
232	26e		H	3-(3-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl)propanoic acid	$^1\text{H}$ NMR (DMSO- $d_6$ ) $\delta$ (ppm): 9.91 (s, 1H), 7.89 (s, 1H), 7.84 (d, $J$ = 7.0 Hz, 1H), 7.52 (d, $J$ = 2.2 Hz, 1H), 7.48 to 7.46 (m, 2H), 7.44 to 7.41 (m, 2H), 7.39 (dd, $J$ = 8.2 Hz, 1H), 7.32 (dd, $J$ = 3.5 Hz, 1H), 7.08 (dd, $J$ = 5.1, 3.5 Hz, 1H), 6.95 (d, $J$ = 8.4 Hz, 1H), 2.92 (t, $J$ = 7.6 Hz, 2H), 2.62 (t, $J$ = 7.6 Hz, 2H). LRMS: 366.10 (calc) 367.1 (obs)
233	26f	H		2,2,2-trifluoroacetic acid compound with 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)benzoic acid (1:1)	$^1\text{H}$ NMR (DMSO- $d_6$ ) $\delta$ (ppm): 10.03 (s, 1H), 8.09 (q, $J$ = 8.6 Hz, 4H), 7.51 (d, $J$ = 2.0 Hz, 1H), 7.40 (dd, $J$ = 4.9, 0.98 Hz, 1H), 7.37 (dd, $J$ = 8.2, 2.2 Hz, 1H), 7.30 (dd, $J$ = 3.3, 0.78 Hz, 1H), 7.07 (dd, $J$ = 5.1, 3.5 Hz, 1H), 6.90 (d, $J$ = 8.4 Hz, 1H). LRMS: 338.1 (calc) 339.0 (obs).
234	26g	H		N1-(2-amino-5-(thiophen-2-yl)phenyl)-N4-hydroxyterephthalamide	$^1\text{H}$ NMR (DMSO- $d_6$ ) $\delta$ (ppm): 9.84 (s, 1H), 8.06 (d, $J$ = 8.4 Hz, 2H), 7.87 (d, $J$ = 8.4 Hz, 2H), 7.47 (d, $J$ = 2.2 Hz, 1H), 7.36 (dd, $J$ = 5.1, 1.2 Hz, 1H), 7.31 (dd, $J$ = 8.4, 2.3 Hz, 1H), 7.25 (dd, $J$ = 3.5, 1.2 Hz, 1H), 7.05 (dd, $J$ = 5.1, 3.5 Hz, 1H), 6.81 (d, $J$ = 8.4 Hz, 1H), 5.21 (s, 2H). LRMS: 353.1 (calc) 354.0 (obs).

Cpd	Ex	R <sub>1</sub>	R <sub>2</sub>	Name	Characterization
235	26h	H		methyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)benzoate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.94 (s, 1H), 8.11 (q, J= 8.4 Hz, 4H), 7.47 (d, J= 2.2 Hz, 1H), 7.36 (dd, J= 5.1, 0.98 Hz, 1H), 7.31 (dd, J= 8.4, 2.2 Hz, 1H), 7.25 (dd, J= 3.5, 0.98 Hz, 1H), 7.05 (dd, J= 5.1, 3.7 Hz, 1H), 6.81 (d, J= 8.2 Hz, 1H), 5.22 (s, 2H), 3.90 (s, 3H). LRMS: 352.1 (calc) 353.0 (obs)

## Example 27a

(S)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-((3-(dimethylamino)-2,5-dioxopyrrolidin-1-yl)methyl)benzamide (242)

## Scheme 27



Step 1: (S)-4-((3-(Benzyloxycarbonylamino)-2,5-dioxopyrrolidin-1-yl)methyl)benzoic acid (238)

[0860] A mixture of *N*-carbobenzyloxy-L-aspartic anhydride (236) (546 mg, 2.19 mmol) and 4-(aminomethyl)benzoic acid hydrochloride (237) (383 mg, 2.53 mmol) was suspended in pyridine (8 mL) and treated with triethylamine (1 mL). The white suspension was stirred at room temperature for 9 h then concentrated under reduced pressure. The residue was dissolved in acetic acid and stirred at 83 °C for 24 h, concentrated, diluted with DCM, washed with an



aqueous solution of KHSO<sub>4</sub> and H<sub>2</sub>O then concentrated. The residue was diluted once again with benzene, concentrated and the remaining yellow solid was triturated with MeOH/H<sub>2</sub>O (1:1) to give title compound 238 (471 mg, 56% yield).

[0861] LRMS: 382.1 (calc) 383.0 (M+H)

Step 2: (S)-4-((3-Amino-2,5-dioxopyrrolidin-1-yl)methyl)benzoic acid (239)

[0862] Following the same procedure as described in Example 1, step 3 (scheme 1), but substituting AcOEt for a 2:1 mixture of isopropanol-ethylacetate, title compound 239 was obtained in quantitative yield.

[0863] LRMS: 248.1 (calc) 249.0 (M+H)

Step 3: (S)-4-((3-(Dimethylamino)-2,5-dioxopyrrolidin-1-yl)methyl)benzoic acid (240)

[0864] To a solution of the amino acid **239** (305 mg, 1.23 mmol) in 96% formic acid (30 mL), MeOH (15 mL) and H<sub>2</sub>O (5 mL) was added solid formaldehyde (77.2 mg, 25.7 mmol) and the mixture was stirred at 70 °C for 3.5 h then more formaldehyde was added (579 mg, 19.3 mmol) and the reaction was further stirred at 70 °C for 4 h. The reaction mixture was cooled to 40 °C, stirred under vacuum for 20 h and evaporated under reduced pressure. The residue was suspended in dry MeOH/benzene and the solvents were removed under reduced pressure. The suspension-evaporation procedure was repeated two more times, to provide title compound 240 (339 mg, quantitative yield). The material was used without additional purification in the next step.

[0865] LRMS: 276.1 (calc) 277.0 (M+H)

Step 4: (S)-tert-Butyl 2-(4-((3-(dimethylamino)-2,5-dioxopyrrolidin-1-yl)methyl)benzamido)-4-(thiophen-2-yl)phenylcarbamate (241)

[0866] Following the same procedure as described in Example 1, step 6 (scheme 1), but substituting compound **7** for compound 240, title compound 241 was obtained in 17% yield (over two steps).

[0867] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.90 (s, 1H), 8.74 (s, 1H), 7.93 (d, J= 8.2 Hz, 2H), 7.80 (d, J= 2.2 Hz, 1H), 7.62 (d, J= 8.6 Hz, 1H), 7.54 to 7.50 (m, 2H), 7.45 (dd, J= 3.5, 0.98 Hz, 1H), 7.40 (d, J= 8.4 Hz, 2H), 7.13 (dd, J= 5.1, 3.5 Hz, 1H), 4.65 (s, 2H), 3.95 (dd, J= 8.6, 4.7 Hz, 1H), 2.89 to 2.69 (m, 2H), 2.25 (s, 6H), 1.45 (s, 9H).

Step 5: (S)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-((3-(dimethylamino)-2,5-dioxopyrrolidin-1-yl)methyl)benzamide (242)

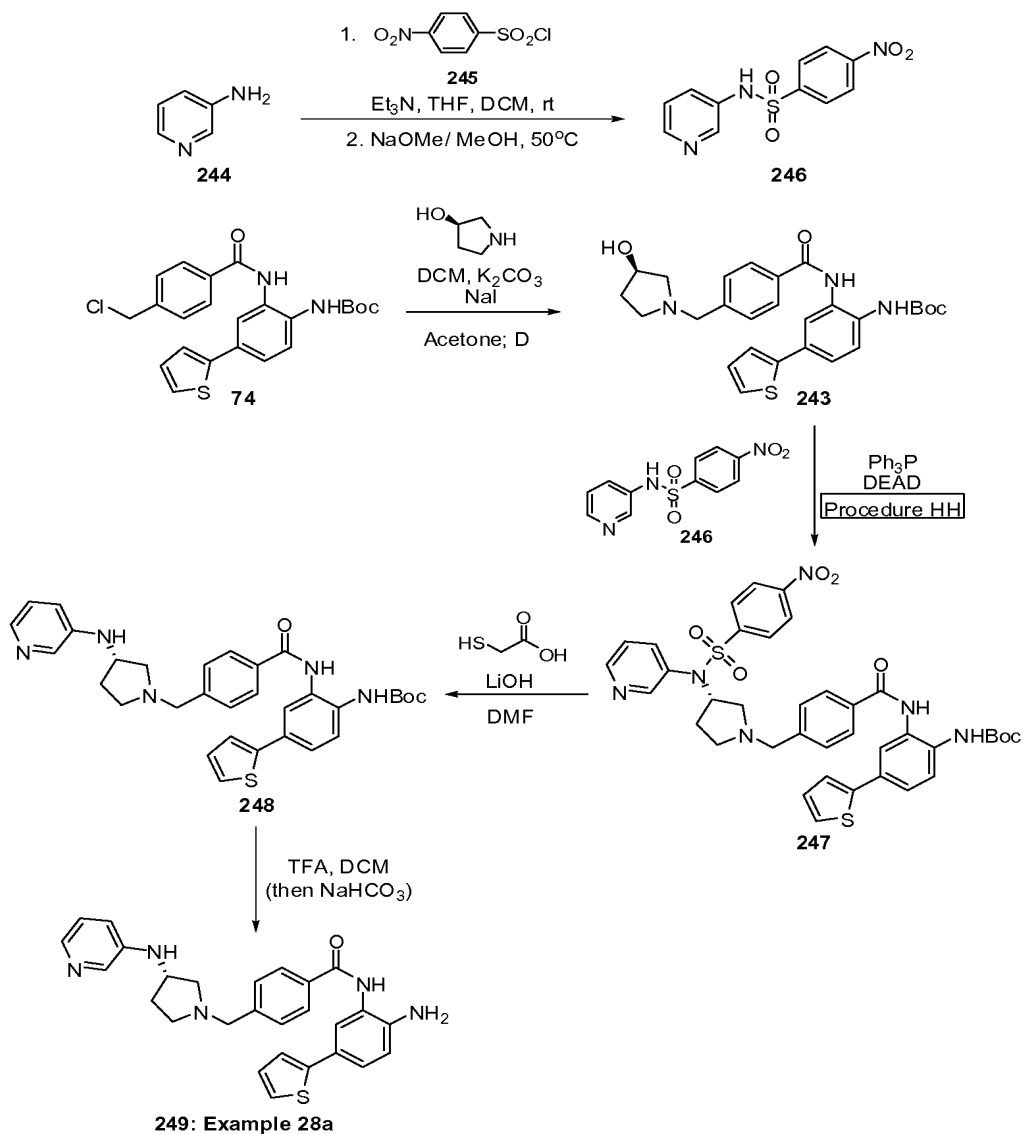
**[0868]** Following the same procedure as described in Example 1, Step 7, but substituting compound **8** for compound **241**, the title compound 242 was obtained (81% yield).

**[0869]** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.71 (s, 1H), 7.95 (d, J= 8.2 Hz, 2H), 7.46 (d, J= 2.2 Hz, 1H), 7.38 to 7.35 (m, 3H), 7.30 (dd, J= 8.4, 2.2 Hz, 1H), 7.24 (dd, J= 3.5, 1.2 Hz, 1H), 7.05 (dd, J= 5.1, 3.5 Hz, 1H), 6.80 (d, J= 8.4 Hz, 1H), 5.16 (s, 2H), 4.64 (s, 2H), 3.95 (dd, J= 8.6, 4.7 Hz, 1H), 2.89 to 2.82 (m, 1H), 2.74 to 2.68 (m, 1H), 2.25 (s, 6H).

#### **Example 28a**

**(S)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-((3-(pyridin-3-ylamino)pyrrolidin-1-yl)methyl)benzamide (249)**

## Scheme 28



Step 1: (R)-tert-Butyl 2-(4-((3-hydroxypyrrolidin-1-yl)methyl)benzamido)-4-(thiophen-2-yl)phenylcarbamate (**243**)

[0870] Following the same procedure as described in Example 6, step 2 (scheme 6), but substituting (S)-2-(methoxymethyl)pyrrolidine for (R)-pyrrolidin-3-ol (0.173 g, 1.99 mmol), compound 243 was obtained in quantitative yield.

[0871] LRMS: 493.2 (calc) 494.2 (obs)

Step 2: 4-Nitro-*N*-(pyridin-3-yl)benzenesulfonamide (**246**)

[0872] To a solution of 3-aminopyridine **244** (3.03 g, 32.23 mmol) in THF (70 mL) and DCM (135 mL) was added 4-nitrobenzene sulfonyl chloride **245** (1.5 g, 67.68 mmol), triethylamine (7.17 g, 70.9 mmol) and dimethylamino pyridine (catalytic amount). The reaction mixture was allowed to stir at room temperature for 1 h then concentrated. The residue was taken up in MeOH (200 mL) then solid sodium methoxide (20 g) was added and the reaction mixture was stirred at 50 °C for 3 h, carefully neutralized with 1N HCl until pH 7. The formed precipitate was collected by filtration to give the title compound **246** (7.67 g, 85% yield).

[0873] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 10.88 (s, 1H), 8.36 (d, *J*=9.0 Hz, 2H), 8.28 (dd, *J*=6.1, 1.4 Hz, 1H), 8.27 (d, *J*=2.5 Hz, 1H), 7.50 (ddd, *J*=8.4, 2.7, 1.6 Hz, 1H), 7.30 (ddd, *J*=8.2, 4.7, 0.8 Hz, 1H).

Step 3: (S)-*tert*-Butyl 2-(4-((3-(4-nitro-*N*-(pyridin-3-yl)phenylsulfonamido)pyrrolidin-1-yl)methyl)benzamido)-4-(thiophen-2-yl)phenylcarbamate (**247**)

[0874] To a solution of **243** (0.98 g, 1.81 mmol) in THF (10 mL) at 0 °C, was added compound **246** (0.61 g, 2.17 mmol), triphenylphosphine (0.76 g, 2.89 mmol) and diethyl azodicarboxylate (DEAD) (0.51 g, 2.90 mmol), the ice bath was removed and the reaction mixture was allowed to stir at room temperature for 18 h. The reaction mixture was partitioned between EtOAc and H<sub>2</sub>O, organic phase was collected, washed successively with saturated NH<sub>4</sub>Cl and brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give a light brown oil which was purified by flash chromatography (eluent: 50% AcOEt in hexanes to 100% AcOEt) to give intermediate **247** (0.65 g, 47% yield).

[0875] <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ (ppm): 9.84 (s, 1H), 8.71 (s, 1H), 8.65 (dd, *J*=4.5, 1.4 Hz, 1H), 8.40 (d, *J*=9.0 Hz, 2H), 8.30 (d, *J*=2.3 Hz, 1H), 7.96 (d, *J*=9.0 Hz, 2H), 7.82 (d, *J*=8.4 Hz, 2H), 7.80 (d, *J*=2.2 Hz, 1H), 7.96 (d, *J*=9.0 Hz, 2H), 7.82 (d, *J*=8.4 Hz, 2H), 7.80 (d, *J*=2.2 Hz, 1H), cannot evaluate this region because of the presence of residual Ph<sub>3</sub>PO (7.63-7.51), 7.48 (dd, *J*=9.2, 4.7 Hz, 1H), 7.44 (dd, *J*=3.5, 1.2 Hz, 1H), 7.12 (dd, *J*=5.1, 3.5 Hz, 1H), 7.09 (d, *J*=8.0 Hz, 2H), 4.85 (bs, 1H), 3.49 (d, *J*=13.9 Hz, 1H), 3.39 (d, *J*=13.7 Hz, 1H), 2.57-2.54 (m, 1H), 2.47-2.43 (m, 1H), 2.37-2.31 (m, 1H), 2.19-2.14 (m, 1H), 1.65-1.60 (m, 1H), 1.43-1.40 (m, 1H).

Step 4: (S)-tert-Butyl 2-(4-((3-(pyridin-3-ylamino)pyrrolidin-1-yl)methyl)benzamido)-4-(thiophen-2-yl)phenylcarbamate (248)

[0876] To a solution of **247** (0.65 g, 0.86 mmol) in DMF (5 mL) was added mercaptoacetic acid (0.103 g, 1.12 mmol) followed by solid lithium hydroxide (0.108 g, 2.58 mmol). The reaction mixture was allowed to stir at room temperature for 18 h and then at 70 °C for 4h. The reaction mixture was concentrated, diluted with AcOEt and extracted with H<sub>2</sub>O, saturated NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give a yellow oil which was purified by flash chromatography (eluents: 100% EtOAc then 2.5% MeOH/1% Et<sub>3</sub>N/96.5% EtOAc and finally, 5% MeOH/1% Et<sub>3</sub>N/94% EtOAc) to provide title compound **248** (0.333 g, 68 % yield).

[0877] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.87 (s, 1H), 8.73 (s, 1H), 7.92 (d, J=7.8 Hz, 2H), 7.91 (d, J=3.7 Hz, 1H), 7.79 (d, J=2.0 Hz, 1H), 7.72 (dd, J=4.5, 1.2 Hz, 1H), 7.59 (d, J=8.6 Hz, 1H), 7.52-7.46 (m, 4H), 7.43 (dd, J=3.5, 1.0 Hz, 1H), 7.11 (dd, J=5.1, 3.5 Hz, 1H), 7.03 (d, J=8.3, 4.5 Hz, 1H), 6.85 (dd, J=8.6, 1.2 Hz, 1H), 6.00 (d, J=7.0 Hz, 1H), 3.93-3.87 (m, 1H), 3.72 (d, J=13.3 Hz, 1H), 3.63 (d, J=13.5 Hz, 1H), 2.79 (dd, J=9.2, 7.0 Hz, 1H), 2.66 (d, J=5.9 Hz, 1H), 2.48-2.44 (m, 1H), 2.37 (dd, J=9.2, 4.1 Hz, 1H), 2.26-2.19 (m, 1H), 1.62-1.58 (m, 1H).

Step 5: (S)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-((3-(pyridin-3-ylamino)pyrrolidin-1-yl)methyl)benzamide (249)

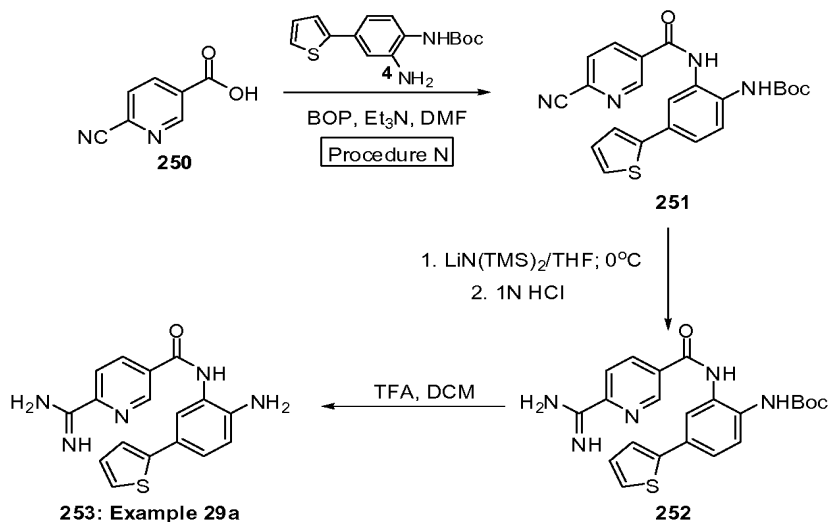
[0878] Following the procedure as described in Example 1, step 7 (scheme 1), but substituting compound **8** for compound **248**, the title compound **249** was obtained (0.14g, 51% yield).

[0879] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.69 (s, 1H), 7.94 (d, J=8.0 Hz, 2H), 7.92 (d, J=2.5 Hz, 1H), 7.72 (d, J=3.9 Hz, 1H), 7.45-7.43 (m, 3H), 7.33 (dd, J=5.1, 1.2 Hz, 1H), 7.28 (dd, J=8.4, 2.2 Hz, 1H), 7.22 (dd, J=3.5, 1.0 Hz, 1H), 7.05-7.02 (m, 2H), 6.85 (ddd, J=8.2, 2.7, 1.6 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 6.00 (d, J=6.8 Hz, 1H), 5.14 (s, 2H), 3.95-3.86 (m, 1H), 3.70 (d, J=13.5 Hz, 1H), 3.62 (d, J=13.5 Hz, 1H), 2.80 (t, J=8.4 Hz, 1H), 2.65 (q, J=5.5 Hz, 1H), 2.48-2.44 (m, 1H), 2.37 (dd, J=10.0, 4.5 Hz, 1H), 2.23 (sext, J=8.0 Hz, 1H), 1.59 (sext, J=6.3 Hz, 1H).

**Example 29a**

**N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-carbamimidoylbenzamide (253)**

Scheme 29



**Step 1: *tert*-Butyl 2-(6-cyanonicotinamido)-4-(thiophen-2-yl)phenylcarbamate (251)**

[0880] Following the same procedure as described in Example 1, step 6 (scheme 1), but substituting compound 7 for compound 250, and pyridine for triethyl amine and DMF, title compound 251 was obtained (41% yield).

[0881]  $^1\text{H NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$  (ppm): 10.22 (s, 1H), 9.25 (d,  $J = 1.6$  Hz, 1H), 8.84 (s, 1H), 8.53 (dd,  $J = 8.0, 2.4$  Hz, 1H), 8.24 (d,  $J = 8.0$  Hz, 1H), 7.28 (dd,  $J = 3.6, 1.2$  Hz, 1H), 7.75-7.71 (m, 2H), 7.54-7.50 (m, 2H), 7.43 (dd,  $J = 3.6, 1.2$  Hz, 1H), 7.11 (dd,  $J = 5.2, 3.6$ , 1H), 1.43 (s, 9H).

**Step 2 *tert*-Butyl 2-(6-carbamimidoylnicotinamido)-4-(thiophen-2-yl)phenylcarbamate (252)**

[0882] To a 1M solution of lithium bis(trimethylsilyl)amide in THF (0.076 mL, 0.76 mmol) at 0 °C was added compound **251** (0.10g, 0.24 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 18 h, cooled to 0 °C, treated with 1N HCl (15 mL), stirred for 30 min and concentrated. The residue was diluted with AcOEt and extracted with  $\text{H}_2\text{O}$ . The aqueous phase was collected, neutralized with 1N NaOH, extracted with AcOEt, dried over  $\text{MgSO}_4$ , filtered and concentrated. The resulting brown solid was triturated with diethyl ether to give intermediate **252** (50 mg, 48% yield).

[0883] LRMS: 437.5 (calc) 438.0 (obs)

Step 3: *N*-(2-Amino-5-(thiophen-2-yl)phenyl)-6-carbamimidoylnicotinamide (253)

[0884] Following the procedure as described in Example 1, step 7 (scheme 1), but substituting compound **8** for compound **252**, the title compound **253** was obtained in 5% yield [after purification by prep HPLC (eluent: 30% MeOH to 70% MeOH in water).

[0885] <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ (ppm): 9.37 (d, J=1.6 Hz, 1H), 8.65 (dd, J=8.0, 2.0, 1H), 8.32 (d, J=8.4 Hz, 1H), 7.52 (d, J=2.0 Hz, 1H), 7.40-7.38 (m, 1H), 7.25 (dd, J=5.2, 0.8 Hz, 1H), 7.22 (d, J=3.2 Hz, 1H), 7.03 (dd, J=4.8, 3.2 Hz, 1H), 6.92 (d, J=8.0 Hz, 1H).

**Example 30a**

**4-(2-Amino-5-(3-oxocyclopent-1-enyl)phenylcarbamoyl)phenyl acetate (260)**

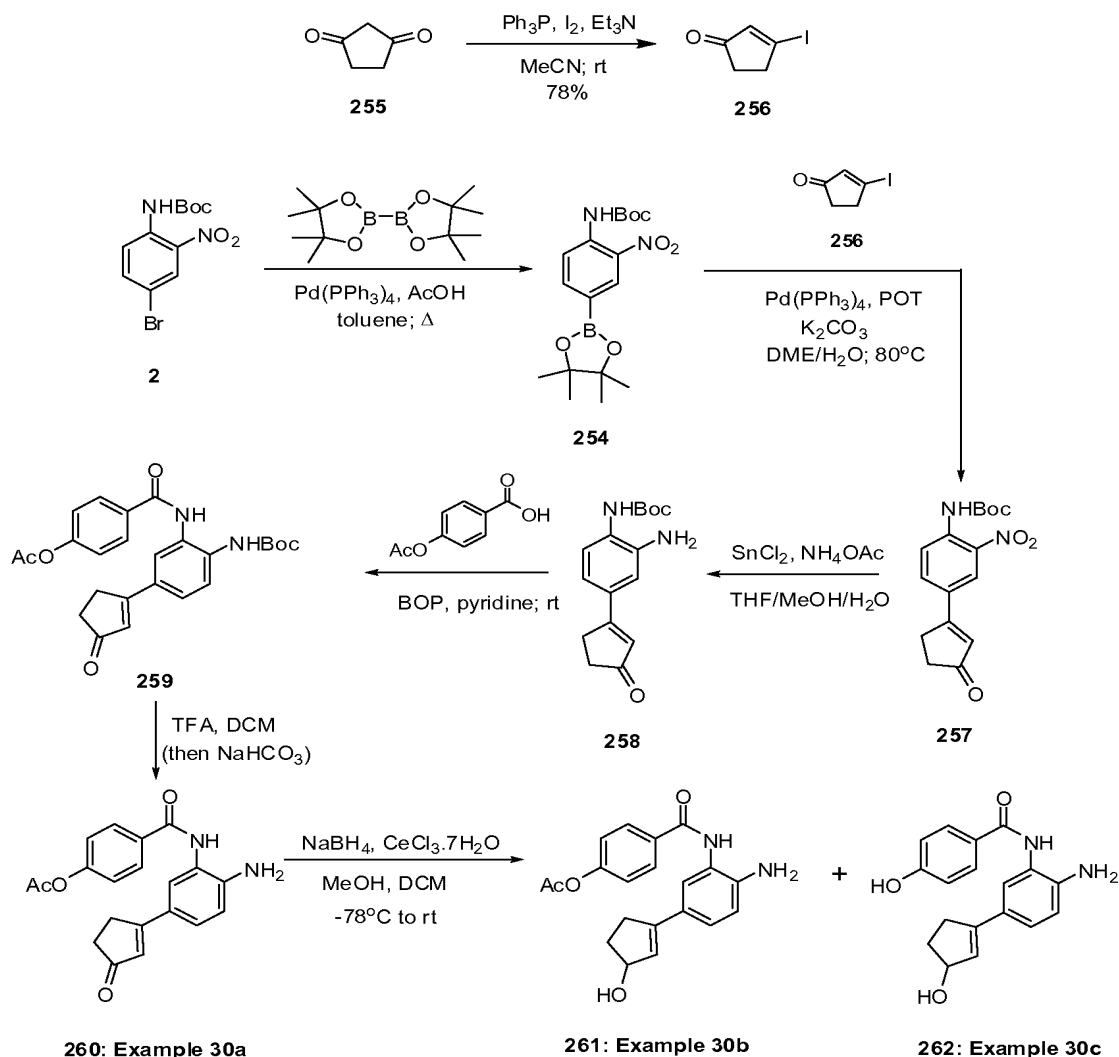
**Example 30b**

**4-(2-Amino-5-(3-hydroxycyclopent-1-enyl)phenylcarbamoyl)phenyl acetate (261)**

**Example 30c**

***N*-(2-Amino-5-(3-hydroxycyclopent-1-enyl)phenyl)-4-hydroxybenzamide (262)**

## Scheme 30



**Step 1: *tert*-Butyl 2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (254)**

**[0886]** To a degassed solution of bromide **2** (1 g, 3.16 mmol), bis(pinacolate)diborane (1.6 g, 6.32 mmol) and acetic acid (0.93 g, 9.5 mmol) in toluene (30 mL) was added tetrakis(triphenyl) phosphine (0.1 g, 0.64 mmol) and the reaction mixture was immediately heated to 120 °C for 2 h. The reaction mixture was cooled to room temperature, washed with H<sub>2</sub>O, brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by flash chromatography to provide title compound **254** as a yellow solid (0.9 g, 78% yield).



[0887]  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 9.80 (s, 1H), 8.61 (d,  $J$ = 1.6 Hz, 1H), 8.55 (d,  $J$ = 8.4 Hz, 1H), 7.96 (dd,  $J$ = 8.6, 1.6 Hz, 1H), 1.54 (s, 9H), 1.34 (s, 12H). LRMS: 364.16 (calc) 387.1 (M + Na, obs).

Step 2: 3-Iodocyclopent-2-enone (256)

[0888] A solution of iodine (6.2 g, 24.5 mmol) and triphenylphosphine (6.6 g, 26.5 mmol) in acetonitrile (200 mL) was stirred at room temperature for 2 h followed by the addition of cyclopentane-1,3-dione **255** (2 g, 20.6 mmol) and triethylamine (2.5 g, 24.5 mmol). The reaction mixture was stirred at 110 °C for 3 h then cooled to room temperature, concentrated and then purified by flash chromatography (eluent: 60% AcOEt in hexanes) to provide title compound **256** as a white solid (3.3 g, 78% yield).

[0889]  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 6.65 (t,  $J$ = 2.0 Hz, 1H), 3.06 to 3.03 (m, 2H), 2.47 to 2.45 (m, 2H).

Step 3: *tert*-Butyl 2-nitro-4-(3-oxocyclopent-1-enyl)phenylcarbamate (257)

[0890] Following the same procedure as described in Example 1, step 2 (scheme 1), but substituting compound **2** for compound **256** and 2-thiophene boronic acid for **254**, title compound **257** was obtained as a yellow solid in 96% yield [after flash chromatography (eluent: 20% AcOEt in hexanes)].

[0891] LRMS: 318.2 (calc) 319.0 (obs).

Step 4: *tert*-Butyl 2-amino-4-(3-oxocyclopent-1-enyl)phenylcarbamate (258)

[0892] Following the same procedure as described in Example 14a, step 4 (scheme 14), but substituting compound **146** for compound **257**, title compound **258** was obtained (quantitative yield).

Step 5: 4-(2-(*tert*-Butoxycarbonylamino)-5-(3-oxocyclopent-1-enyl)phenylcarbamoyl)phenyl acetate (259)

[0893] Following the same procedure as described in Example 1, step 6 (scheme 1), but substituting compound **4** for compound **258** and compound **7** for 4-acetoxybenzoic acid, title compound **259** was obtained as a yellow oil in 30% yield [after flash chromatography (eluent: 30% AcOEt in hexanes)].

[0894] LRMS: 450.2 (calc) 473.0 (obs)

Step 6: 4-(2-Amino-5-(3-oxocyclopent-1-enyl)phenylcarbamoyl)phenyl acetate (**260**)

[0895] Following the same procedure as described in Example 1, step 7 (scheme 1), but substituting compound **8** for compound **259**, the title compound **260** was obtained as a yellow solid (89% yield).

[0896]  $^1\text{H}$  NMR: ( $\text{CD}_3\text{OD}$ )  $\delta$  (ppm): 8.07 (d,  $J=8.0$  Hz, 2H), 7.62 (d,  $J=1.2$  Hz, 1H), 7.54 (dd,  $J=5.2, 1.2$  Hz, 1H), 7.24 (d,  $J=8.1$  Hz, 2H), 6.90 (d,  $J=8.0$  Hz, 1H), 6.43 (s, 1H), 3.09 (m, 2H), 2.50 (m, 2H), 2.31 (s, 3H). LRMS: 350.4 (calc) 351 (obs)

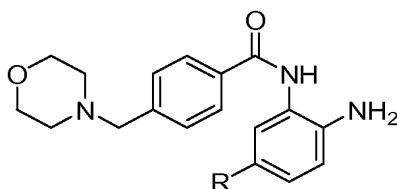
Step 7: 4-(2-Amino-5-(3-hydroxycyclopent-1-enyl)phenylcarbamoyl)phenyl acetate (**261**) and *N*-(2-amino-5-(3-hydroxycyclopent-1-enyl)phenyl)-4-hydroxybenzamide (**262**)

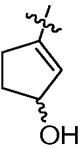
[0897] To a stirring solution of amine **260** (0.11 g, 6.31 mmol) in DCM (9 mL) and cerium (III) chloride heptahydrate (0.37 g, 0.93 mmol) in MeOH (6 mL) at  $-78^\circ\text{C}$  was added sodium borohydride (60 mg, 0.93 mmol) in one portion. The reaction mixture was allowed to warm to room temperature and stirred for 15 min then concentrated. Purifications by flash chromatography (eluent: 5% MeOH in DCM) followed by chromatotron (same eluent) provided the title compounds **261** (15 mg, 14% yield) and **262** (15 mg, 16% yield).

[0898] Compound **261**:  $^1\text{H}$  NMR: ( $\text{CD}_3\text{OD}$ )  $\delta$  (ppm): 8.08 (d,  $J=8.1$  Hz, 2H), 7.37 (s, 1H), 7.30 (dd,  $J=5.1, 1.2$ , 1H), 7.27 (d,  $J=8.2$  Hz, 2H), 6.87 (d,  $J=8.2$  Hz, 1H), 6.13 (s, 1H), 4.61 (m, 1H), 3.31 (m, 3H), 2.81 (m, 1H), 2.61 (m, 1H), 2.32 (s, 3H), 1.91 (m, 1H). LRMS: 352.14 (calc) 335.0 (M-OH, obs)

[0899] Compound **262**:  $^1\text{H}$  NMR: ( $\text{CD}_3\text{OD}$ )  $\delta$  (ppm): 7.88 (d,  $J=8.1$  Hz, 2H), 7.33 (m, 1H), 7.27 (dd,  $J=5.2, 1.1$  Hz, 1H), 6.88 (m, 3H), 6.13 (s, 1H), 4.61 (s, 1H), 3.34 (s, 3H), 2.81 (m, 1H), 2.61 (m, 1H), 2.31 (m, 1H), 2.12 (s, 1H), 1.92 (m, 1H).

Table 15: Characterization of compounds prepared according to Scheme 30.

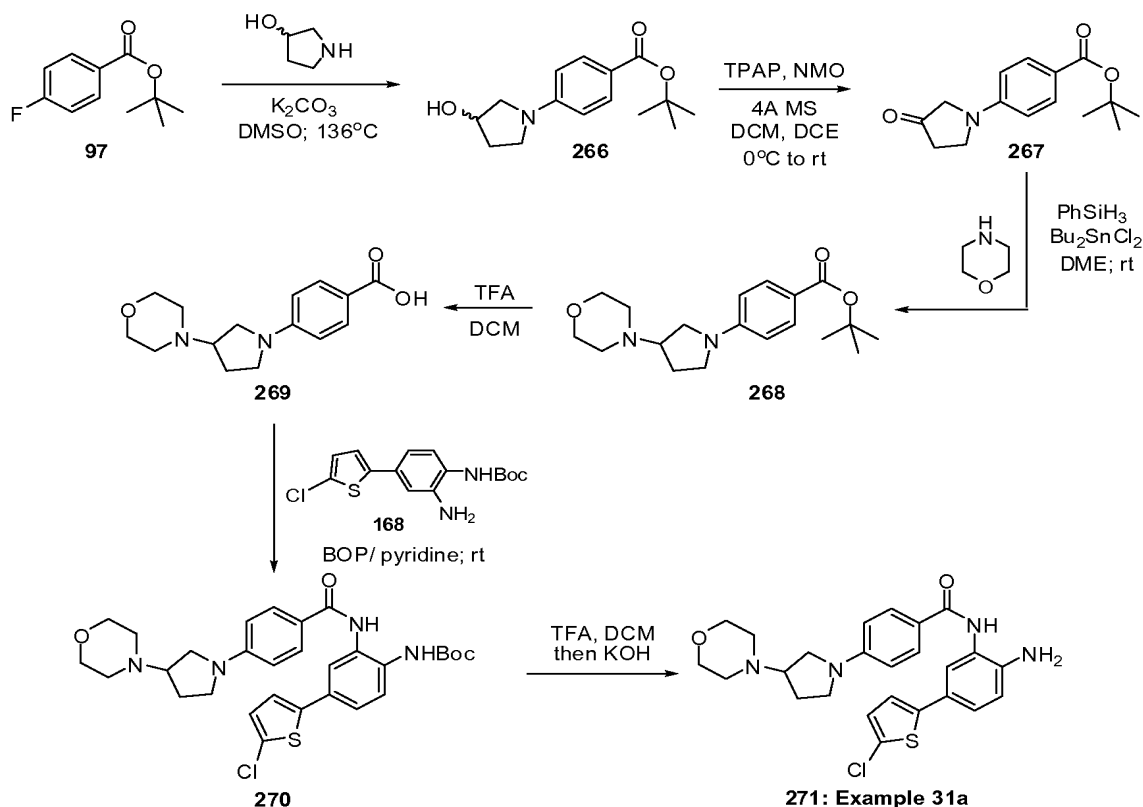


Cpd	Ex	R	Name	Characterization
265	30f		N-(2-amino-5-(3-hydroxycyclohex-1-enyl)phenyl)-4-(morpholinomethyl)benzamide	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 8.12 (s, 1H), 7.85 (d, J=8.0 Hz, 2H), 7.42 (d, J=8.1 Hz, 2H), 7.34 (s, 1H), 7.20 (dd, J=8.4, 2.2 Hz, 1H), 6.73 (d, J=9.1 Hz, 1H), 6.18 (s, 1H), 4.59 (s, 1H), 3.70 (t, J=5.1 Hz, 4H), 3.57 (s, 2H), 3.32 (s, 3H), 2.72 (m, 1H), 2.49 (m, 4H), 2.29 (m, 1H), 2.12 (s, 2H), 1.90 (m, 1H). LRMS: 393.21 (calc) 376.0 (found)M-18 (deoxygenation).

### Example 31a

### *N*-(2-Amino-5-(5-chlorothiophen-2-yl)phenyl)-4-(3-morpholinopyrrolidin-1-yl)benzamide (271)

#### Scheme 31



#### Step 1: *tert*-Butyl 4-(3-hydroxypyrrolidin-1-yl)benzoate (266)

[0900] A mixture of fluoride **97** (2.24 g, 11.4 mmol), pyrrolidin-3-ol (1.37 g, 15.8 mmol) and potassium carbonate (2.24 g) was suspended in dimethyl sulfoxide (5 mL) and stirred at 136 °C for 7 h. The reaction mixture was cooled to room temperature, diluted with DCM, washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, filtered and concentrated to provide title compound **266** (3.93 g, 100%).

[0901] LRMS: 263.3 (calc) 264.1 (obs)

Step 2: *tert*-Butyl 4-(3-oxopyrrolidin-1-yl)benzoate (267)

[0902] A mixture of alcohol **266** (2.75 g, 10.45 mmol), NMO (5.8 g, 49 mmol) and 4Å molecular sieves (8.34 g) was suspended in dry DCM (100 mL) and dry 1,2-dichloroethane (100 mL), stirred at room temperature for 45 min, and then cooled to 0 °C for the addition of solid TPAP (0.36 g, 1.03 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 5 h, filtered through Celite®/silica gel using 50% AcOEt in hexanes as an eluent, then concentrated. The residue was purified by flash chromatography (eluent: 30% to 50% AcOEt in hexane) to provide title compound **267** (0.78 g, 29% yield).

[0903] LRMS: 261.3 (calc) 284.1 (M+Na, obs)

Step 3: *tert*-Butyl 4-(3-morpholinopyrrolidin-1-yl)benzoate (268)

[0904] A mixture of ketone **267** (0.40 g, 1.53 mmol), dibutyltin dichloride (0.35 g) and morpholine (0.27 mL) in ethyleneglycol dimethylether (3.5 mL) was stirred at room temperature for 6 h, then cooled to 0 °C for the addition of neat phenyl silane (0.60 mL, 4.72 mmol). The reaction mixture was stirred at room temperature for 18 h then diluted with MeOH (3 mL) and H<sub>2</sub>O (0.5 mL), stirred for additional 4 h and concentrated. The residue was purified by flash chromatography (eluent: 5% MeOH in DCM) to provide title compound **268** (0.56 g, >100% yield, crude, used without additional purification).

[0905] LRMS: 332.2 (calc) 333.2 (obs)

Step 4: 4-(3-Morpholinopyrrolidin-1-yl)benzoic acid (269)

[0906] Following the same procedure as described in Example 8, step 2 (scheme 8), but substituting compound **98** for compound **268**, title compound **269** was obtained (used as is in the next reaction).

[0907] MS: 276.1 (calc) 277.1 (obs)

Step 5: *tert*-Butyl 2-(4-(3-morpholinopyrrolidin-1-yl)benzamido)-4-(thiophen-2-yl)phenylcarbamate (270)

[0908] Following the same procedure as described in Example 1, step 6 (scheme 1), but substituting compound **4** for compound **168** and compound **7** for compound **269**, title compound **270** was obtained in 40% yield.

[0909] LRMS: 582.2 (calc) 583.0 (obs)

Step 6: *N*-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(3-morpholinopyrrolidin-1-yl)benzamide (271)

[0910] Following the same procedure as described in Example 1, step 7 (scheme 1), but substituting compound **8** for compound **270**, the title compound **271** was obtained in 40% yield.

[0911] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.42 (s, 1H), 7.87 (d, J= 9.0 Hz, 2H), 7.40 (d, J= 2.2 Hz, 1H), 7.22 (dd, J= 8.4, 2.3 Hz, 1H), 7.11 (d, J= 3.9 Hz, 1H), 7.05 (d, J= 3.9 Hz, 1H), 6.80 (d, J= 8.4 Hz, 1H), 6.60 (d, J= 8.8 Hz, 2H), 5.17 (s, 2H), 3.61 (t, J= 4.5 Hz, 4H), 3.57-3.55 (m, 1H), 3.47 (t, J= 8.6 Hz, 1H), 3.32-3.28 (m, 1H), 3.12 (t, J= 8.2 Hz, 1H), 2.97-2.89 (m, 1H), 2.47 (m, 4H, overlapped with DMSO-d<sub>6</sub>), 2.25-2.19 (m, 1H), 1.88-.78 (m, 1H). LRMS: 482.2 (calc) 483.0 (obs).

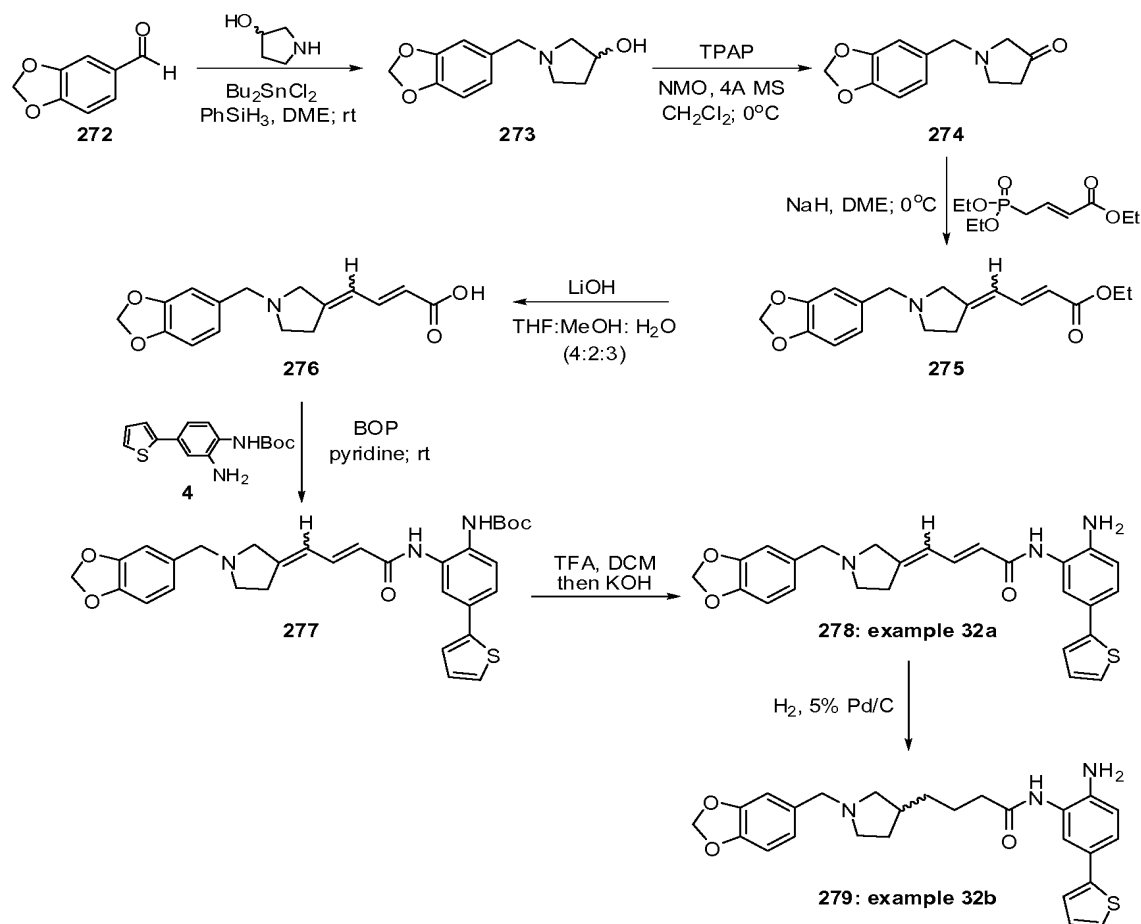
**Example 32a**

**(2E,4E)-*N*-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-ylidene)but-2-enamide (278)**

**Example 32b**

***N*-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-yl)butanamide (279)**

Scheme 32



#### Step 1: 1-(Benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-ol (273)

**[0912]** A solution of pyrrolidin-3-ol (0.539 g, 6.2 mmol) in ethyleneglycol dimethylether (DME) (5 mL) was treated with benzo[d][1,3]dioxole-5-carbaldehyde (272) (1.08 g, 7.2 mmol) and dibutylchlorostannane (0.71 g, 2.3 mmol). After the suspension was stirred for 15 min at room temperature, phenylsilane (1.0 mL, 8.6 mmol) was added neat and the mixture was stirred for 18 h. The reaction mixture was diluted with DCM (50 mL), treated with 1N HCl (13 mL) and stirred for 30 min followed by dilution with H<sub>2</sub>O (50 mL) and DCM (50 mL). The aqueous layer was collected, basified with solid potassium carbonate (K<sub>2</sub>CO<sub>3</sub>), extracted with DCM, dried over MgSO<sub>4</sub>, filtered and concentrated to provide title compound 273 (0.82 g, 60% yield).

**[0913]** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 6.85 to 6.81 (m, 2H), 6.73 (dd, J= 8.0, 1.8 Hz, 1H), 5.97 (s, 2H), 4.69 (d, J= 4.3 Hz, 1H), 4.18 to 4.16 (m, 1H), 3.44 (q, J= 12.9 Hz, 2H), 2.62 (dd, J=

9.8, 6.3 Hz, 1H), 2.55-2.50 (m, 1H), 2.39-2.33 (m, 1H), 2.28 to 2.25 (m, 1H), 2.01-1.93 (m, 1H), 1.55-1.48 (m, 1H).

Step 2: 1-(Benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-one (274)

[0914] A solution of alcohol **273** (0.78 g, 3.53 mmol) in dry DCM (40 mL) was treated with 4Å molecular sieves (powder, 3.49 g) and 4-methylmorpholine N-oxide (NMO) (2.11 g, 18.03 mmol) and the suspension was stirred under nitrogen atmosphere for 18 h. The reaction mixture was cooled to 0 °C for the addition of solid tetrapropylammonium perruthenate (TPAP) (0.11 g, 0.31 mmol) and stirred for 30 min, then diluted with DCM, filtered through a Celite® pad, washed with saturated NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered through a pad of SiO<sub>2</sub> (eluent: 5% MeOH in DCM) and concentrated to provide title compound **274** (0.65 g, 84% yield).

[0915] LRMS: 219.18 (calc) 219.9 (obs)

Step 3: (2E,4E)-Ethyl 4-(1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-ylidene)but-2-enoate (275)

[0916] To a solution of ketone **274** (0.65 g, 2.96 mmol) and (E)-ethyl 4-(diethoxyphosphoryl)but-2-enoate (1.0 mL, 4.33 mmol) in ethyleneglycol dimethylether (50 mL) at 0 °C was added NaH (0.26 g, 6.58 mmol) and the mixture was stirred at 0 °C for 30 min then at room temperature for 2 h. The reaction mixture was quenched with acetone (2 mL) then diluted with DCM and washed with saturated NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by flash column chromatography (eluent: 50% AcOEt in DCM) to provide title compound **275** (0.15 g, 16% yield) as a mixture of cis/trans isomers.

[0917] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 7.26 (dd, J= 15.3, 11.5 Hz, 0.5H), 7.12 (dd, J= 15.1, 11.5 Hz, 0.5H), 6.88-6.83 (m, 2H), 6.77 (dt, J= 9.2, 1.6 Hz, 1H), 6.14 (t, J= 11.7 Hz, 1H), 5.99 (d, J= 2.9 Hz, 2H), 5.83 (d, J= 15.2 Hz, 1H), 4.14-4.07 (m, 2H), 3.53 (d, J= 19.2 Hz, 2H), 3.30 (s, 1H), 3.16 (s, 1H), 2.61 (s, 2H), 2.57 (d, J= 5.3 Hz, 1H), 1.22-1.18 (m, 4H).

Step 4: (2E,4E)-4-(1-(Benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-ylidene)but-2-enoic acid (276)

[0918] A solution of ester **275** (0.15 g, 0.485 mmol) in 2:1 THF: MeOH (6 mL) was treated with a solution of lithium hydroxide (59 mg, 1.41 mmol) in H<sub>2</sub>O (3 mL) and stirred for 18 h. The reaction mixture was quenched with 1N HCl (2.0 mL), concentrated, diluted with H<sub>2</sub>O, cooled to -78 °C and lyophilized to provide title compound **276** (quantitative, in a mixture with LiCl).

[0919] LRMS: 287.1 (calc) 288.0 (obs)

Step 5: *tert*-Butyl 2-((2E,4E)-4-(1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-ylidene)but-2-enamido)-4-(thiophen-2-yl)phenylcarbamate (277)

[0920] Following the same procedure as described in Example 1, step 6 (scheme 1), but substituting compound **7** for compound **276**, title compound **277** was obtained (71% yield) [after column chromatography (eluent: 5% isopropanol in DCM)].

[0921] LRMS: 229.21 (calc) 560.1 (obs)

Step 6: (2E,4E)-*N*-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-ylidene)but-2-enamide (278)

[0922] Following the same procedure as described in Example 1, step 7 (scheme 1), but substituting compound **8** for compound **277** and sodium bicarbonate with potassium hydroxide, the title compound **278** was obtained in quantitative yield.

[0923] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.32 (s, 0.5H), 9.31 (s, 0.5H), 7.65 (d, J= 8.2 Hz, 1H), 7.35 (d, J= 5.1 Hz, 1H), 7.25-7.18 (m, 3H), 7.05-7.03 (m, 1H), 6.90-6.84 (m, 2H), 6.81-6.74 (m, 2H), 6.18 to 6.12 (m, 2H), 5.99 (s, 2H), 5.17 (s, 1H), 5.16 (s, 1H), 3.56 (s, 1H), 3.51 (s, 1H), 3.29 (s, 1H), 3.17 (s, 1H), 2.63 to 2.59 (s, 4H).

Step 7: *N*-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(1-(benzo[d][1,3]dioxol-5-ylmethyl)pyrrolidin-3-yl)butanamide (279)

[0924] Following the same procedure as described in Example 1, step 3 (scheme 1), but substituting compound **3** for compound **278**, and 10% palladium on carbon for 5% palladium on carbon, title compound **279** in 20% yield.

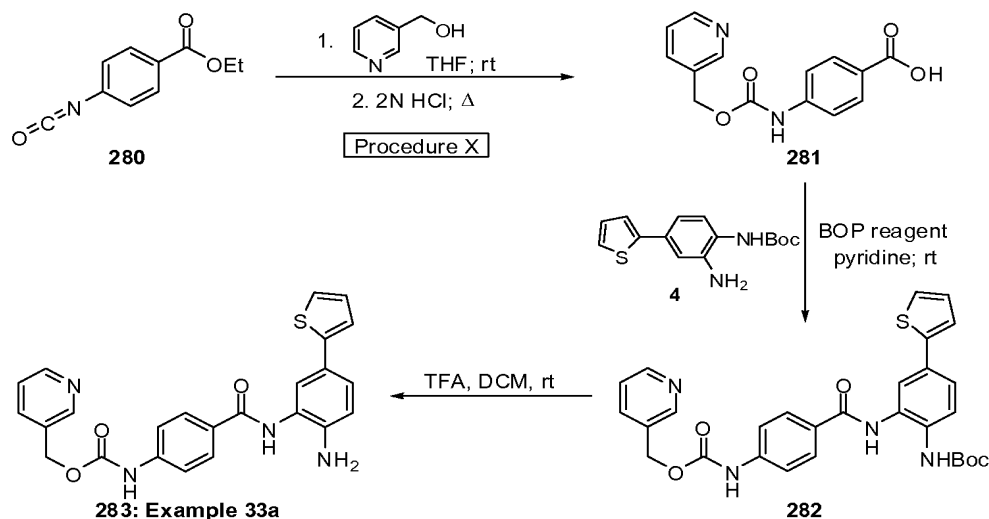
[0925] LRMS: 463.2 (calc) 464.0 (obs)

### Example 33a

**Pyridin-3-ylmethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate (283)**



Scheme 33



Step 1: 4-((Pyridin-3-ylmethoxy)carbonylamino)benzoic acid (281)

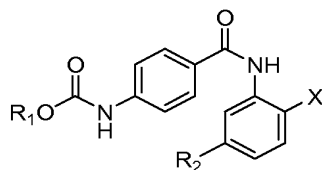
[0926] A solution of ethyl 4-isocyanatobenzoate **280** (2.0 g, 10.46 mmol) and pyridin-3-ylmethanol in THF was stirred at room temperature for 18 h then concentrated. The crude material was taken up in 2N HCl, heated to reflux for 16 h then cooled to -78 °C and lyophilized to give a solid material which was triturated with acetone to give title compound **281** (3.098 g, 96% yield).

[0927] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 10.27 (s, 1H), 8.88 (s, 1H), 8.79 (d, J= 3.3 Hz, 2H), 7.86 (d, J= 8.8 Hz, 3H), 7.56 (d, J= 8.8 Hz, 2H), 5.32 (s, 2H).

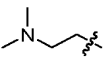
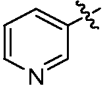
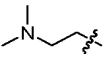
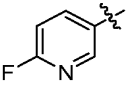
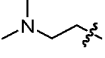
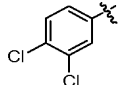
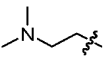
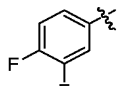
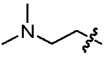
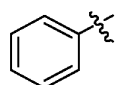
Steps 2 & 3: Pyridin-3-ylmethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate (283)

[0928] Following the same procedure as described in Example 1, steps 6 and 7 (scheme 1), using compound **4** but substituting compounds **7** & **8** for compounds **281** & **282**, the title compound **283** was obtained (step 2: 31% yield, step 3: 23% yield).

[0929] <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ (ppm): 10.11 (s, 1H), 9.61 (s, 1H), 8.66 (s, 1H), 8.55 (dd, J= 4.7, 1.6 Hz, 1H), 7.93 (d, J= 8.6 Hz, 2H), 7.86 (d, J= 8.2 Hz, 1H), 7.57 (d, J= 8.8 Hz, 2H), 7.44-7.41 (m, 2H), 7.33 (dd, J= 5.1, 0.98 Hz, 1H), 7.27 (dd, J= 8.2, 2.2 Hz, 1H), 7.22 (dd, J= 3.5, 1.2 Hz, 1H), 7.03 (dd, J= 5.1, 3.7 Hz, 1H), 6.79 (d, J= 8.4 Hz, 1H), 5.22 (s, 2H), 5.13 (s, 2H).

Table 16: Characterization of compounds **284-296** prepared according to Scheme 33

Cpd	Ex	R <sub>1</sub>	R <sub>2</sub>	X	Name	Characterization
284	33b			NH <sub>2</sub>	(tetrahydro-2H-pyran-2-yl)methyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.06 (1H,s), 9.59 (1H,s), 7.92 (2H,d,8.8), 7.57 (2H,d,8.6 Hz), 7.44 (1H,s), 7.34 (1H,d,5.1 Hz), 7.27 (1H,d,8.2 Hz), 7.23 (1H,d,3.5 Hz), 7.03 (1H,t, 3.7 Hz), 6.79 (1H,d,8.4 Hz), 5.12 (2H,s), 4.09 - 4.00 (2H,m), 3.89 - 3.86 (1H,m), 3.54 (1H,m), 1.80 (1H,m), 1.60 - 1.56 (1H,m), 1.48 (3H,m), 1.32 - 1.23 (2H,m) LRMS: 451.2 (calc) 452.2 (obs).
285	33c			NH <sub>2</sub>	2-(dimethylamino)ethyl 4-(2-amino-5-(thiophen-3-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 7.97 (d, J=8.2 Hz, 2H), 7.62 (d, J=8.1 Hz, 2H), 7.50 (s, 1H), 7.42 (m, 4H), 6.92 (d, J=8.0 Hz, 1H), 4.31 (t, J=5.6 Hz, 2H), 2.69 (t, J= 5.51 Hz, 2H), 2.31 (s, 6H). LRMS: 424.16 (calc) 425.0 (obs).
286	33d			NH <sub>2</sub>	2-(dimethylamino)ethyl 4-(4-amino-4'-chloro-5'-fluorobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR: (CD <sub>3</sub> OD) δ (ppm): 7.97 (d, J=8.1 Hz, 2H), 7.61 (d, J=8.0 Hz, 2H), 7.45 (m, 3H), 7.37 (m, 2H), 6.94 (d, J=8.1 Hz, 1H), 4.30 (t, J=5.2 Hz, 2H), 2.69 (t, J=5.2 Hz, 2H), 2.32 (s, 6H). LRMS: 470.9 (calc) 471.0 (obs).
287	33e			NH <sub>2</sub>	2-(dimethylamino)ethyl 4-(4-amino-5'-fluorobiphenyl-3-ylcarbamoyl)phenylcarbamate hydrochloride	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 7.98 (d, J=8.0 Hz, 2H), 7.62 (d, J=8.0 Hz, 2H), 7.49 (m, 1H), 7.39 (m, 3H), 7.30 (s, 1H), 7.66 (d, J=8.1 Hz, 2H), 4.49 (t, J=5.1 Hz, 2H), 3.47 (t, J=5.1 Hz, 2H), 2.88 (s, 6H). LRMS: 436.19 (calc) 437 (obs).
288	33f			NH <sub>2</sub>	2-(dimethylamino)ethyl 4-(2-amino-5-(6-chloropyridin-3-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.01 (s, 1H), 9.62 (s, 1H), 8.61 (d, J=2.1 Hz, 1H), 8.01 (dd, J=7.2, 1.3 Hz, 1H), 7.92 (d, J=8.1 Hz, 2H), 7.61 (m, 3H), 7.49 (d, J=8.1 Hz, 1H), 7.39 (m, 1H), 6.88 (d, J=5.6 Hz, 1H), 5.25 (s, 2H), 4.18 (t, J=5.2 Hz, 2H), 3.34 (s, 1H), 2.51 (t, J=5.1 Hz, 2H), 2.19 (s, 6H). LRMS: 453.92 (calc) 454.0 (obs).

Cpd	Ex	R <sub>1</sub>	R <sub>2</sub>	X	Name	Characterization
289	33g			NH <sub>2</sub>	2-(dimethylamino)ethyl 4-(2-amino-5-(pyridin-3-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 8.78 (s, 1H), 8.40 (s, 1H), 8.00 (m, 3H), 7.62 (d, J=8.0 Hz, 2H), 7.53 (d, J=3.5 Hz, 1H), 7.42 (m, 2H), 7.01 (d, J=8.1 Hz, 1H), 4.51 (t, J=5.1 Hz, 2H), 3.42 (t, J=5.2 Hz, 2H), 2.91 (s, 6H). LRMS: 419.48 (calc) 420.1 (obs).
290	33h			NH <sub>2</sub>	2-(dimethylamino)ethyl 4-(2-amino-5-(6-fluoropyridin-3-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.1 (s, 1H), 9.62 (s, 1H), 8.40 (s, 1H), 8.13 (m, 1H), 7.92 (d, J=8.0 Hz, 2H), 7.58 (d, J=8.1 Hz, 2H), 7.52 (s, 1H), 7.32 (dd, J=7.9, 2.1 Hz, 1H), 7.18 (dd, J=8.0, 1.8 Hz, 1H), 6.89 (d, J=8.1 Hz, 1H), 5.20 (s, 1H), 4.18 (t, J=5.1 Hz, 2H), 3.33 (s, 1H), 2.51 (t, J=5.1 Hz, 2H), 2.18 (s, 6H). LRMS: 437.47 (calc) 438.0 (obs).
291	33i			NH <sub>2</sub>	2-(dimethylamino)ethyl 4-(4-amino-4',5'-dichlorobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.05 (s, 1H), 9.62 (s, 1H), 7.91 (d, J=8.01 Hz, 2H), 7.78 (s, J=1.3 HZ, 1H), 7.55 (m, 4H), 7.33 (m, 1H), 6.82 (d, J=7.2 Hz, 1H), 5.22 (s, 1H), 4.18 (t, J=5.1 Hz, 2H), 2.52 (t, J=5.1 Hz, 2H), 2.18 (s, 6H). LRMS: 487.38 (calc) 487.0 (obs).
292	33j			NH <sub>2</sub>	2-(dimethylamino)ethyl 4-(4-amino-4',5'-difluorobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.01 (s, 1H), 9.61 (s, 1H), 7.92 (d, J=8.1 Hz, 2H), 7.58 (m, 3H), 7.50 (s, 1H), 7.39 (m, 3H), 6.81 (d, J=8.1 Hz, 1H), 5.18 (s, 2H), 4.18 (t, J=5.1 Hz, 2H), 2.51 (t, J=5.0 Hz, 2H), 2.18 (s, 6H). LRMS: 454.47 (calc) 455.0 (obs).
293	33k			NH <sub>2</sub>	2-(dimethylamino)ethyl 4-(4-aminobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.01 (s, 1H), 9.68 (s, 1H), 7.92 (d, J=8.2 Hz, 2H), 7.54 (m, 4H), 7.49 (s, 1H), 7.37 (m, 2H), 7.31 (m, 1H), 7.21 (m, 2H), 6.82 (d, J=7.9 Hz, 1H), 5.01 (s, 2H), 4.19 (t, J=5.1 Hz, 2H), 2.53 (t, J=5.1 hz, 2H), 2.20 (s, 6H). LRMS: 418.49 (calc) 419.1 (obs).


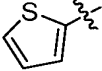

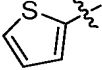

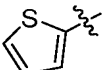
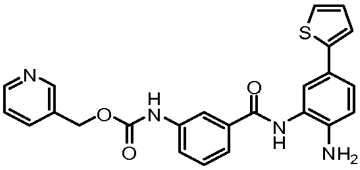
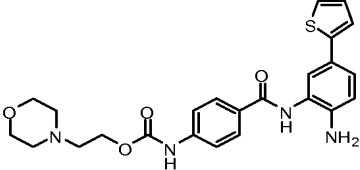
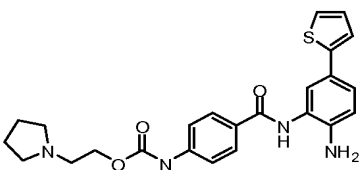
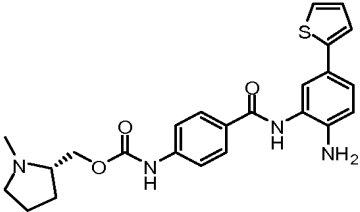
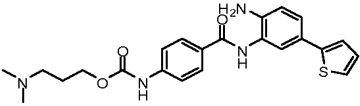
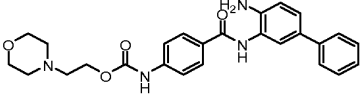
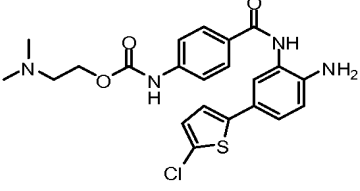
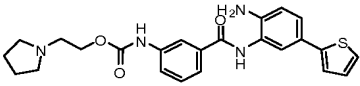
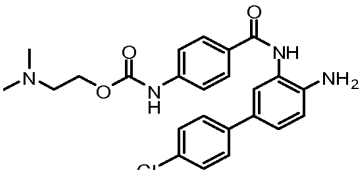
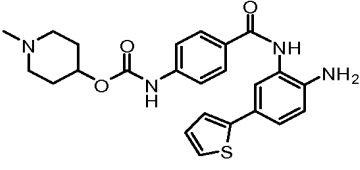
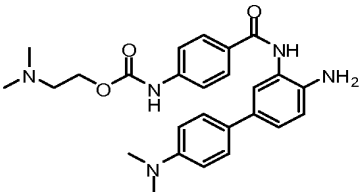
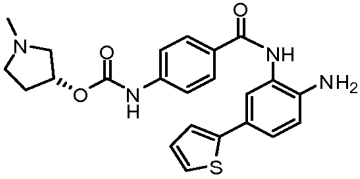
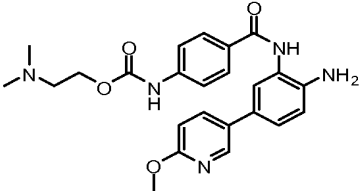
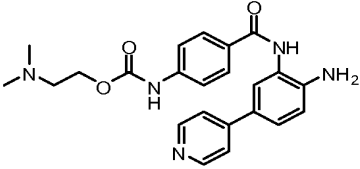
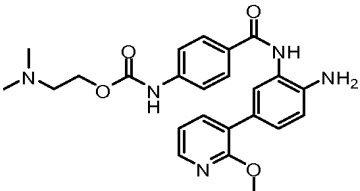
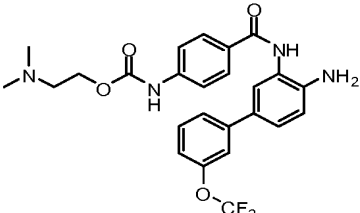
Cpd	Ex	R <sub>1</sub>	R <sub>2</sub>	X	Name	Characterization
294	33i			NH <sub>2</sub>	2-(methylpyridin-2-yl)aminoethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.03 (s,1H), 9.62 (s,1H), 8.67 (ddd, J1=4.8 Hz, J2=2.0Hz, J3=0.8 Hz, 1H), 7.94 (d, J=8.8 Hz, 2H), 7.57 (d, J=8.8 Hz, 2H), 7.50 (ddd, J1=16.0 Hz, J2=7.2 Hz, J3=2.0 Hz, 1H), 7.46 (d, J=2.0 Hz, 1H), 7.36 (dd, J1=5.2 Hz, J2=1.2 Hz, 1H), 7.29 (dd, J1=8.4 Hz, J2=2.0 Hz, 1H), 7.24 (dd, J1=3.6 Hz, J2=1.2 Hz, 1H), 7.05 (dd, J1=5.2 Hz, J2=3.6 Hz, 1H), 6.80 (d, J=8.4 Hz, 1H), 6.65 (d, J=8.8 Hz, 1H), 6.56 (ddd, J1=7.6 Hz, J2=4.8 Hz, J3=0.8 Hz, 1H), 5.14 (s, 2H), 4.28 (t, J=6.0 Hz, 2H), 3.84 (t, J=6.0 Hz, 2H), 3.06 (s, 3H). LRMS: 487.57 (calc) 488.0 (obs).
295	33m			NH <sub>2</sub>	2-(4-methylpiperazin-1-yl)ethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.03 (s,1H), 9.62 (s,1H), 7.95 (d, J=8.8 Hz, 2H), 7.60 (d, J=8.8 Hz, 2H), 7.46 (d, J=2.4 Hz, 1H), 7.36 (dd, J1=5.2 Hz, J2=0.8 Hz, 1H), 7.29 (dd, J1=8.0 Hz, J2=2.0 Hz, 1H), 7.24 (dd, J1=3.6 Hz, J2=1.2 Hz, 1H), 7.05 (dd, J1=4.8 Hz, J2=3.6 Hz, 1H), 6.80 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 2.59 (t, J=5.6 Hz, 2H), 2.57-2.16 (m, 7H, overlapped DMSO-d <sub>6</sub> ), 2.16 (s, 4H). LRMS: 479.59 (calc) 480.1 (obs).
296	33n			OH	2-(dimethylamino)ethyl 4-(2-hydroxy-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.07 (s, 1H), 9.47 (s, 1H), 8.00(s, 1H), 7.92-7.94 (m, 2H), 7.83(dt, 1H), 7.59-7.61 (m, 2H), 7.54 (dt, 1H), 7.42 (dd, 1H), 7.27-7.35 (m, 3H), 7.07 (dd, 1H), 6.94 (d, 1H), 4.24 (t, 2H), 2.74 (t, 2H), 2.35 (s, 6H). No J? LRMS 425.14 (calc) 426 (obs).

Table 16a: Characterization of compounds prepared according to Scheme 33

Cpd	Ex	R	Name	Characterization
585	33o		pyridin-3-ylmethyl 3-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.11 (s, 1H), 9.09 (d, J=2.4 Hz, 1H), 9.05 (d, J=1.6 Hz, 1H), 8.57 (t, J=2.0 Hz, 1H), 7.78 (dd, J1=3.8 Hz, J2=1.0 Hz, 1H), 7.72 (dd, J1=5.2 Hz, J2=1.2 Hz, 1H), 7.49 (d, J=2.4 Hz, 1H), 7.36 (dd, J1=5.2 Hz, J2=1.2 Hz, 1H), 7.33 (dd, J1=8.6 Hz, 1H), 7.25 (m, 2H), 7.05 (dd, J1=5.2 Hz, J2=3.6 Hz, 1H), 6.82 (d, J=8.4 Hz, 1H), 5.31 (s, 2H). LRMS: 444.51(calc) 445.0 (found)
586	33p		2-morpholinoethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.04 (s, 1H), 9.63 (s, 1H), 7.95 (d, J1=8.8 Hz, 2H), 7.59 (d, J=8.8 Hz, 2H), 7.45 (d, J1=2.0 Hz, 1H), 7.36 (dd, J1=5.2 Hz, J2=1.2 Hz, 1H), 7.29 (dd, J1=8.4 Hz, J2=2.0 Hz, 1H), 7.24 (dd, J1=3.6 Hz, J2=1.2 Hz, 1H), 7.05 (dd, J1=5.2 Hz, J2=3.6 Hz, 1H), 6.80 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 4.22 (t, J=5.6 Hz, 2H), 3.57 (t, J=4.8 Hz, 4H), 2.59 (t, J=5.6 Hz, 2H), 2.44 (s, 4H). LRMS: 466.55 (calc) 467.0 (found)
587	33q		2-(pyrrolidin-1-yl)ethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.06 (s, 1H), 9.63 (s, 1H), 7.95 (d, J1=8.8 Hz, 2H), 7.60 (d, J=8.8 Hz, 2H), 7.45 (d, J1=2.0 Hz, 1H), 7.36 (dd, J1=5.2 Hz, J2=1.2 Hz, 1H), 7.29 (dd, J1=8.4 Hz, J2=2.0 Hz, 1H), 7.24 (dd, J1=3.6 Hz, J2=1.2 Hz, 1H), 7.05 (dd, J1=5.2 Hz, J2=3.6 Hz, 1H), 6.80 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 4.24 (s, 2H), 2.92-2.42 (m, 6H, overlapped DMSO-d <sub>6</sub> ), 1.73 (s, 4H). LRMS: 450.55 (calc) 451.0 (found)

Cpd	Ex	R	Name	Characterization
588	33r		(S)-(1-methylpyrrolidin-2-yl)methyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.99 (s, 1H), 9.63 (s, 1H), 7.95 (d, J=8.8 Hz, 2H), 7.58 (d, J=8.8 Hz, 2H), 7.46 (d, J1=2.0 Hz, 1H), 7.36 (dd, J1=5.2 Hz, J2=1.2 Hz, 1H), 7.29 (dd, J1=8.4 Hz, J2=2.0 Hz, 1H), 7.24 (dd, J1=3.6 Hz, J2=1.2 Hz, 1H), 7.05 (dd, J1=4.8 Hz, J2=3.6 Hz, 1H), 6.80 (d, J=8.4 Hz, 1H), 4.14-4.01 (m, 2H), 2.96 (m, 1H), 2.54-2.41 (m, 1H, overlapped DMSO-d <sub>6</sub> ), 2.35 (s, 3H), 2.24-2.12 (m, 1H), 1.97-1.87 (m, 1H), 1.72-1.55 (m, 3H). LRMS: 450.55 (calc) 451.0 (found)
589	33s		3-(dimethylamino)propyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.95 (s, 1H), 9.62 (s, 1H), 7.95 (d, J=8.8 Hz, 2H), 7.59 (d, J=8.8 Hz, 2H), 7.46 (d, J=2.0 Hz, 1H), 7.35 (dd, J1=5.2 Hz, J2=1.2 Hz, 1H), 7.29 (dd, J1=8.4 Hz, J2=2.0 Hz, 1H), 7.24 (dd, J1=3.6 Hz, J2=1.2 Hz, 1H), 7.04 (dd, J1=5.0 Hz, J2=3.4 Hz, 1H), 6.81 (d, J=8.4 Hz, 1H), 5.13 (s, 2H), 4.14 (t, J=6.6 Hz, 2H), 2.31 (t, J=7.0 Hz, 2H), 2.14 (s, 6H), 1.77 (p, J=6.9 Hz, 2H). LRMS: 438.17 (calc) 439.2 (found)
343	33t		2-morpholinoethyl 4-(4-aminobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.03 (s, 1H), 9.63 (s, 1H), 7.95 (d, J=8.8 Hz, 2H), 7.60 (d, J=8.4 Hz, 2H), 7.55 (dd, J1=8.4 Hz, J2=1.2, 2H), 7.51 (d, J=2.4 Hz, 1H), 7.39 (t, J=7.8 Hz, 2H), 7.32 (dd, J1=8.2 Hz, J2=2.2 Hz, 1H), 7.24 (tt, J1=7.4 Hz, J2=1.2 Hz, 1H), 6.86 (d, J=8.4 Hz, 1H), 5.08 (s, 2H), 4.23 (t, J=5.6 Hz, 2H), 3.58 (t, J=4.6 Hz, 4H), 2.59 (t, J=5.6 Hz, 2H), 2.44 (bt, J=4.4 Hz, 4H). LRMS: 460.21 (calc) 461.2 (found)
345	33u		2-(dimethylamino)ethyl 4-(2-amino-5-(5-chlorothiophen-2-yl)phenylcarbamoyl)phenylcarbamate	NMR <sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.02(s, 1H), 9.61(s, 1H), 7.94(d, 2H), 7.59(d, 2H), 7.40(d, 1H), 7.23(dd, 1H), 7.11(d, 1H), 7.04(d, 1H), 6.80(d, 1H), 5.22(s, 2H), 4.19(t, 2H), 4.53(t, 2H), 2.20(s, 6H). LRMS: 458.2 (calc) 459.2 (found for M+H)

Cpd	Ex	R	Name	Characterization
346	33v		2-(pyrrolidin-1-yl)ethyl 3-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.89 (s, 1H), 9.72 (s, 1H), 8.06 (s, 1H), 7.65 (t, J=10.0 Hz, 2H), 7.48 (d, J=2.0 Hz, 1H), 7.42 (t, J=8.0 Hz, 1H), 7.36 (dd, J <sub>1</sub> =5.0 Hz, J <sub>2</sub> =0.6 Hz, 1H), 7.30 (dd, J <sub>1</sub> =8.2 Hz, J <sub>2</sub> =2.2 Hz, 1H), 7.25 (dd, J <sub>1</sub> =3.6 Hz, J <sub>2</sub> =0.8 Hz, 1H), 7.05 (dd, J <sub>1</sub> =5.0 Hz, J <sub>2</sub> =3.4 Hz, 1H), 6.81 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 4.19 (t, J=5.8 Hz, 2H), 2.69 (t, J=5.6 Hz, 2H), 2.49 (m, 4H), 1.68 (p, J=3.2 Hz, 4H). LRMS: 450.17 (calc) 451.2 (found)
347	33w		2-(dimethylamino)ethyl 4-(4-amino-4'-chlorobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.00(s, 1H), 9.61(s, 1H), 7.94(d, 2H), 7.59-7.55(m, 4H), 7.50(d, 1H), 7.42-7.40(m, 2H), 7.31(dd, 1H), 6.84(d, 1H), 5.14(s, 2H), 4.17(t, 2H), 2.52(t, 2H), 2.18(s, 6H). LRMS: (calc.) 452.93 (found) 453.2 (MH)+
348	33x		1-methylpiperidin-4-yl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.92 (s, 1H), 9.61 (s, 1H), 7.92 (d, J=8.4 Hz, 2H), 7.58 (d, J=8.6 Hz, 2H), 7.45 (s, 1H), 7.35 (d, J=4.7 Hz, 1H), 7.28 (m, 2H), 7.05 (m, 1H), 6.81 (d, J=8.3 Hz, 1H), 5.12 (s, 2H), 4.64 (m, 1H), 2.62 (m, 2H), 2.19 (s, 3H), 2.12 (m, 2H), 1.90 (m, 2H), 1.62 (m, 2H). LRMS(ESI): (calc.) 450.55 (found) 451.3 (MH)+
349	33y		2-(dimethylamino)ethyl 4-(4-amino-4'-(dimethylamino)biphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.01 (s, 1H), 9.61 (s, 1H), 7.95 (d, J=8.8 Hz, 2H), 7.60 (d, J=8.8 Hz, 2H), 7.40-7.37 (m, 3H), 7.23 (dd, J <sub>1</sub> =8.4 Hz, J <sub>2</sub> =2.0 Hz, 1H), 6.83-6.75 (m, 3H), 4.90 (s, 2H), 4.20 (t, J=5.6 Hz, 2H), 2.90 (s, 6H), 2.54 (t, J=5.6 Hz, 2H), 2.20 (s, 6H). LRMS: (calc.) 461.6 (found) 462.3 (MH)+

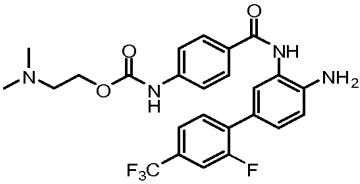
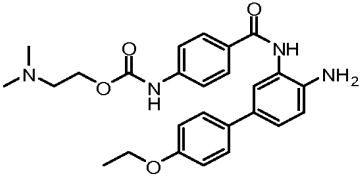
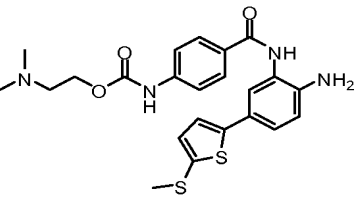
Cpd	Ex	R	Name	Characterization
350	33z		(R)-1-methylpyrrolidin-3-yl 4-(2-amino-5-(thiophen-2-yl)phenyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.01 (s, 1H), 9.63 (s, 1H), 7.92 (d, J=8.5 Hz, 2H), 7.57 (d, J=8.3 Hz, 2H), 7.44 (s, 1H), 7.42 (d, J=4.1 Hz, 1H), 7.22 (m, 2H), 7.05 (m, 1H), 6.81 (d, J=8.4 Hz, 1H), 5.13 (s, 2H), 2.71 (m, 1H), 2.62 (m, 2H), 2.31 (s, 3H), 2.22 (m, 1H), 1.80 (m, 1H). LRMS: (calc.) 436.53 (found) 437.2(MH) <sup>+</sup>
351	33aa		2-(dimethylamino)ethyl 4-(2-amino-5-(6-methoxypyridin-3-yl)phenyl)phenylcarbamate	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.00(s, 1H), 9.63(s, 1H), 8.33(dd, 1H), 7.93(d, 2H), 7.86(dd, 1H), 7.57(dd, 2H), 7.44(d, 1H), 7.27(dd, 1H), 6.83(t, 2H), 5.05(s, 2H), 4.17(t, 2H), 3.85(s, 3H), 2.52(t, 2H), 2.18(s, 6H). LRMS: (calc.) 449.50 (found) 450.3 (MH) <sup>+</sup>
352	33bb		2-(dimethylamino)ethyl 4-(2-amino-5-(pyridin-4-yl)phenyl)phenylcarbamate	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.08(s, 1H), 9.72(s, 1H), 8.03(s, 2H), 7.73(d, 1H), 7.67-7.63(m, 4H), 7.55(dd, 1H), 6.94(d, 1H), 5.43(s, 2H), 4.25(t, 2H), 2.58(t, 2H), 2.26(s, 6H). LRMS: (calc.) 419.59 (found) 420.3 (MH) <sup>+</sup>
353	33cc		2-(dimethylamino)ethyl 4-(2-amino-5-(2-methoxypyridin-3-yl)phenyl)phenylcarbamate	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.00(s, 1H), 9.61(s, 1H), 8.05(dd, 1H), 7.93(d, 2H), 7.64(dd, 1H), 7.57(dd, 2H), 7.38(d, 1H), 7.21(dd, 1H), 7.01(dd, 1H), 6.81(d, 1H), 5.07(s, 2H), 4.17(t, 2H), 3.85(s, 3H), 2.52(t, 2H), 2.18(s, 6H). LRMS: (calc.) 449.5 (found) 450.3 (MH) <sup>+</sup>
354	33dd		2-(dimethylamino)ethyl 4-(4-amino-3'-(trifluoromethoxy)biphenyl-3-yl)phenylcarbamate	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.00(s, 1H), 9.62(s, 1H), 7.94(dd, 2H), 7.61-7.57(m, 3H), 7.55(d, 2H), 7.52-7.48(m, 2H), 7.37(dd, 1H), 7.21-7.19(m, 1H), 6.86(d, 1H), 5.19(s, 2H), 4.19(t, 2H), 2.52(t, 2H), 2.18(s, 6H). LRMS: (calc.) 502.60 (found) 503.2 (MH) <sup>+</sup>



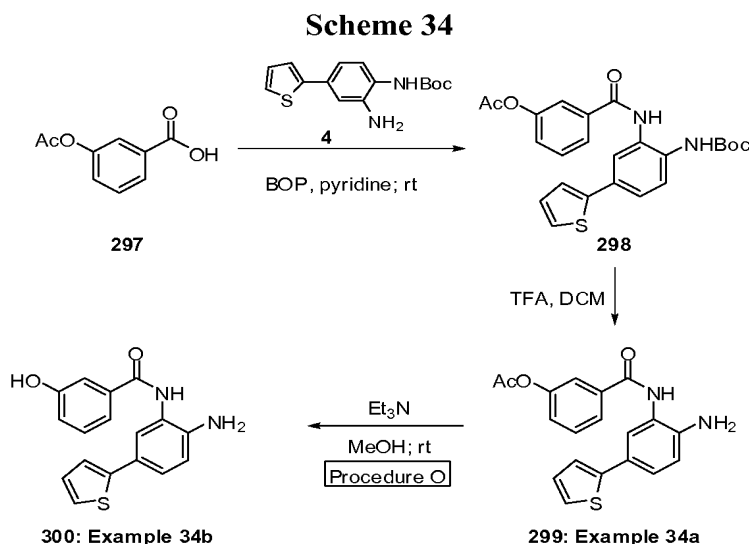
Cpd	Ex	R	Name	Characterization
355	33ee		2-(dimethylamino)ethyl 4-(4-amino-4'-(trifluoromethoxy)biphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.00(s, 1H), 9.61(s, 1H), 7.94(d, 2H), 7.66-7.64(m, 2H), 7.59-7.57(m, 2H), 7.52(d, 1H), 7.36-7.30(m, 3H), 6.85(d, 1H), 5.14(s, 2H), 4.17(t, 2H), 2.52(t, 2H), 2.18(s, 6H). LRMS: (calc.) 502.6 (found) 503.3 (MH)+
356	33ff		2-(dimethylamino)ethyl 4-(4-amino-3'-fluoro-4'-methoxybiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.00(s, 1H), 9.61(s, 1H), 7.94(d, 2H), 7.59-7.57(m, 2H), 7.47(d, 1H), 7.38(dd, 1H), 7.30(dd, 1H), 7.28(dd, 1H), 7.15(t, 1H), 6.82(d, 1H), 5.04(s, 2H), 4.17(t, 2H), 3.82(s, 3H), 2.52(t, 2H), 2.18(s, 6H). LRMS: (calc.) 466.62 (found) 467.3 (MH)+
357	33gg		2-(dimethylamino)ethyl 4-(4-amino-4'-chlorobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.01 (s, 1H), 9.61 (s, 1H), 7.94 (d, J=8.8 Hz, 2H), 7.59-7.54 (m, 4H), 7.47 (d, J=2.2 Hz, 1H), 7.28 (dd, J=8.2, 2.2 Hz, 1H), 7.19 (t, J=8.9 Hz, 1H), 6.84 (d, J=8.2 Hz, 1H), 5.08 (s, 2H), 4.18 (t, J=5.7 Hz, 2H), 2.52 (t, J=5.7 Hz, 2H), 2.19 (s, 6H). LRMS: (calc.) 452.93 (found) 453.2 (MH)+
358	33hh		2-(dimethylamino)ethyl 4-(4-amino-2',4'-difluorobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.01 (s, 1H), 9.61 (s, 1H), 7.94 (d, J=8.8 Hz, 2H), 7.59 (d, 8.8 Hz, 2H), 7.52-7.46 (m, 1H), 7.37 (s, 1H), 7.31-7.25 (m, 1H), 7.18-7.10 (m, 2H), 6.85 (d, J=3.2 Hz, 1H), 5.16 (s, 2H), 4.20 (t, J=5.6 Hz, 2H), 2.57 (t, J=6.0 Hz, 2H), 2.23 (s, 6H). LRMS: (calc.) 454.20 (found) 455.2 (MH)+

Cpd	Ex	R	Name	Characterization
359	33ii		2-(dimethylamino)ethyl 4-(4-amino-4'-(trifluoromethyl)biphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.01 (s, 1H), 9.61 (s, 1H), 7.96 (d, J=8.8 Hz, 2H), 7.75 (dd, J <sub>1</sub> =25.6 Hz, J <sub>2</sub> =8.4 Hz, 4H), 7.61-7.59 (m, 3H), 7.42 (dd, J <sub>1</sub> =8.4 Hz, J <sub>2</sub> =2.0 Hz, 1H), 6.88 (d, J=8.4 Hz, 1H), 5.27 (s, 2H), 4.19 (t, J=6.0 Hz, 2H), 2.52 (t, J=6.0 Hz, 2H), 2.19 (s, 6H). LRMS: (calc.) 486.2 (found) 487.2 (MH)+
360	33jj		2-(dimethylamino)ethyl 4-(4-amino-2'-fluorobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.03 (s, 1H), 9.64 (s, 1H), 7.96 (s, 2H), 7.60 (s, 2H), 7.46-7.42 (m, 2H), 7.30-7.23 (m, 4H), 6.87 (t, J=6.3 Hz, 1H), 4.16 (s, 2H), 4.19 (d, J=4.9 Hz, 2H), 2.5 (m, 2H, overlap with DMSO), 2.20 (s, 6H). LRMS: (calc.) 436.24 (found) 437.2 (MH)+
361	33kk		2-(dimethylamino)ethyl 4-(4-amino-4'-hydroxybiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.08 (s, 1H), 9.70 (s, 1H), 9.46 (s, 1H), 8.03 (m, 3H), 7.60 (s, 2H), 7.41 (m, 3H), 7.26 (m, 1H), 6.85 (m, 2H), 5.01 (s, 2H), 4.20 (s, 2H), 2.50 (s, 2H), 2.10 (s, 6H). LRMS: (calc.) 434.49 (found) 435.2(MH)+
362	33ll		2-(dimethylamino)ethyl 4-(4-amino-3',4',5'-trifluorobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.01 (s, 1H), 9.61 (s, 1H), 7.96 (d, J=8.8 Hz, 2H), 7.60 (d, J=8.8 Hz, 2H), 7.56 (d, J=1.6 Hz, 1H), 7.52 (dd, J <sub>1</sub> =10.0 Hz, J <sub>2</sub> =6.8 Hz, 1H), 7.39 (dd, J <sub>1</sub> =8.4 Hz, J <sub>2</sub> =2.4 Hz, 1H), 6.85 (d, J=8.4 Hz, 1H), 5.26 (s, 2H), 4.20 (t, J=5.6 Hz, 2H), 2.54 (t, J=5.6 Hz, 2H), 2.19 (s, 6H). LRMS: (calc.) 472.5 (found) 473.2 (MH)+
363	33mm		2-(dimethylamino)ethyl 4-(4-amino-4'-(methylthio)biphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.02(s, 1H), 9.63(s, 1H), 7.95(d, 2H), 7.59(dd, 2H), 7.53-7.49(m, 3H), 7.32-7.26(m, 3H), 6.85(d, 1H), 5.07(s, 2H), 4.19(t, 2H), 2.53(t, 2H), 2.48(s, 3H), 2.20(s, 6H). LRMS: (calc.) 464.6 (found) 465.2 (MH)+

Cpd	Ex	R	Name	Characterization
364	33nn		2-(dimethylamino)ethyl 4-(4-amino-4'-cyanobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.02(s, 1H), 9.62(s, 1H), 7.95(d, 2H), 7.83-7.75(m, 4H), 7.63-7.58(m, 3H), 7.44(dd, 1H), 6.88(dd, 1H), 5.34(s, 2H), 4.19(t, 2H), 2.53(t, 2H), 2.20(s, 6H). LRMS: (calc.) 443.5 (found) 444.2 (MH) <sup>+</sup>
365	33oo		2-(dimethylamino)ethyl 4-(4-amino-4'-(4-methoxy-2-fluorophenyl)biphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.00(s, 1H), 9.60(s, 1H), 7.92(d, 2H), 7.57(d, 2H), 7.36-7.32(m, 2H), 7.12(dt, 1H), 6.88-6.80(m, 3H), 5.05(s, 2H), 4.18(t, 2H), 3.77(s, 3H), 2.51(t, 2H), 2.18(s, 6H). LRMS: (calc.) 443.5 (found) 444.2 (MH) <sup>+</sup>
366	33pp		2-(dimethylamino)ethyl 4-(4-amino-2'-fluoro-4'-methoxybiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.01(s, 1H), 9.63(s, 1H), 7.95(d, 2H), 7.58(d, 2H), 7.51(d, 1H), 7.33-7.25(m, 4H), 6.83(d, 1H), 5.11(s, 2H), 4.18(t, 2H), 2.52(t, 2H), 2.21(s, 3H), 2.18(s, 6H). LRMS: (calc.) 466.62 (found) 467.3 (MH) <sup>+</sup>
367	33qq		2-(dimethylamino)ethyl 4-(2-amino-5-(thiazol-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.02(s, 1H), 9.62(s, 1H), 7.95(d, 2H), 7.79(d, 1H), 7.76(d, 1H), 7.60-7.55(m, 4H), 6.83(d, 1H), 5.48(s, 2H), 4.19(t, 2H), 2.52(t, 2H), 2.19(s, 6H). LRMS: (calc.) 425.2 (found) 426.2 (MH) <sup>+</sup>
368	33rr		2-(dimethylamino)ethyl 4-(4-amino-2',4',5'-trifluorobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.01(s, 1H), 9.62(s, 1H), 7.94(d, 2H), 7.61-7.52(m, 4H), 7.41(s, 1H), 7.19(dt, 1H), 6.86(d, 1H), 5.23(s, 2H), 4.19(t, 2H), 2.52(t, 2H), 2.20(s, 6H). LRMS: (calc.) 472.46 (found) 473.3 (MH) <sup>+</sup>

Cpd	Ex	R	Name	Characterization
369	33ss		2-(dimethylamino)ethyl 4-(4-amino-2'-fluoro-4'-(trifluoromethyl)biphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.00(s, 1H), 9.62(s, 1H), 7.94(d, 2H), 7.70-7.67(m, 2H), 7.60-7.57(m, 3H), 7.47(m, 1H), 7.26(dt, 1H), 6.87(d, 1H), 5.31(s, 2H), 4.16(t, 2H), 2.51(t, 2H), 2.18(s, 6H). LRMS: (calc.) 504.59 (found) 505.2 (MH)+
370	33tt		2-(dimethylamino)ethyl 4-(4-amino-4'-ethoxybiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.02 (s, 1H), 9.62 (s, 1H), 7.95 (d, J=8.8 Hz, 2H), 7.59 (d, J=8.8 Hz, 2H), 7.48-7.44 (m, 3H), 7.25 (dd, J1=8.4 Hz, J2=2.4 Hz, 1H), 6.96-6.92 (m, 2H), 6.84 (d, J=8.4 Hz, 1H), 4.98 (s, 2H), 4.19 (t, J=5.6 Hz, 2H), 4.03 (q, J=6.8 Hz, 2H), 2.90 (s, 6H), 2.54 (t, J=5.6 Hz, 2H), 2.20 (s, 6H). LRMS: (calc.) 462.54 (found) 463.2 (MH)+
371	33uu		2-(dimethylamino)ethyl 4-(2-amino-5-(5-(methylthio)thiophen-2-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.02 (s, 1H), 9.61 (s, 1H), 7.94 (d, J=8.8 Hz, 2H), 7.59 (d, J=8.8 Hz, 2H), 7.38 (d, J=2.0 Hz, 1H), 7.20 (dd, J1=8.4 Hz, J2=2.0Hz, 1H), 7.01 (d, J=3.2 Hz, 1H), 6.78 (d, J=8.4 Hz, 1H), 6.73-6.71 (m, 1H), 5.08 (s, 2H), 4.19 (t, J=5.6 Hz, 2H), 2.54 (t, J=5.6 Hz, 2H), 2.42 (s, 3H), 2.20 (s, 6H). LRMS: (calc.) 470.61 (found) 439.2 (MH)+

**Example 34a****3-(2-Amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl acetate (299)****Example 34b****N-(2-Amino-5-(thiophen-2-yl)phenyl)-3-hydroxybenzamide (300)**



Step 1: 3-(2-(*tert*-Butoxycarbonylamino)-5-(thiophen-2-yl)phenylcarbamoyl)phenyl acetate (298)

[0930] Following the same procedure as described in Example 1, step 6 (scheme 1), using compound **4**, but substituting compound **7** for compound **297**, title compound **298** was obtained (81% yield).

[0931]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 9.96 (s, 1H), 8.78 (s, 1H), 7.91 to 7.88 (m, 1H), 7.80 (d,  $J = 2.2$  Hz, 1H), 7.72 (t,  $J = 2.0$  Hz, 1H), 7.64 to 7.59 (m, 2H), 7.54 to 7.51 (m, 2H), 7.46 (dd,  $J = 3.5, 1.2$  Hz, 1H), 7.41 (dd,  $J = 2.3, 0.98$  Hz, 0.5H), 7.39 (dd,  $J = 2.3, 0.98$  Hz, 0.5H), 7.13 (dd,  $J = 5.1, 3.7$  Hz, 1H), 2.32 (s, 3H), 1.46 (s, 9H).

Step 2: 3-(2-Amino-5-(thiophen-2-yl)phenylcarbamoyl)phenyl acetate (296)

[0932] Following the same procedure as described in Example 1, step 7 (scheme 1), but substituting compound **8** for compound **295**, the title compound **296** was obtained (quantitative yield).

[0933]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 9.81 (s, 1H), 7.92 (d,  $J = 8.0$  Hz, 1H), 7.76 (t,  $J = 1.9$  Hz, 1H), 7.57 (t,  $J = 8.0$  Hz, 1H), 7.45 (d,  $J = 2.2$  Hz, 1H), 7.38 to 7.36 (m, 1H), 7.35 (d,  $J = 1.2$  Hz, 1H), 7.31 (dd,  $J = 8.2, 2.2$  Hz, 1H), 7.25 (dd,  $J = 3.7, 1.2$  Hz, 1H), 7.05 (dd,  $J = 5.1, 3.5$  Hz, 1H), 6.81 (d,  $J = 8.2$  Hz, 1H), 5.19 (s, 2H), 2.31 (s, 3H).

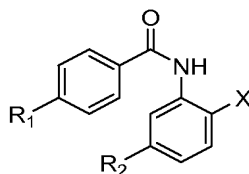
Step 3: *N*-(2-Amino-5-(thiophen-2-yl)phenyl)-3-hydroxybenzamide (297)

[0934] A suspension of acetate **296** (349 mg, 0.99 mmol) in dry MeOH (6 mL) was treated with triethyl amine (1.5 mL) and stirred at room temperature for 19 h, concentrated under

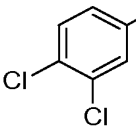
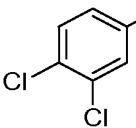
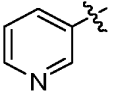
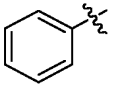
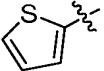
reduced pressure and triturated with diethyl ether to provide the title compound **297** (282.5 mg, 92% yield).

[0935]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 9.72 (s, 1H), 9.66 (s, 1H), 7.47 to 7.43 (m, 2H), 7.37 (s, 2H), 7.35 to 7.31 (m, 2H), 7.27 (d,  $J$ = 16.0 Hz, 1H), 7.05 (d,  $J$ = 2.7 Hz, 1H), 6.97 (d,  $J$ = 7.8 Hz, 1H), 6.81 (d,  $J$ = 8.2 Hz, 1H), 5.13 (s, 2H).

Table 17: Characterization of compounds **301-310** prepared according to Scheme 34.



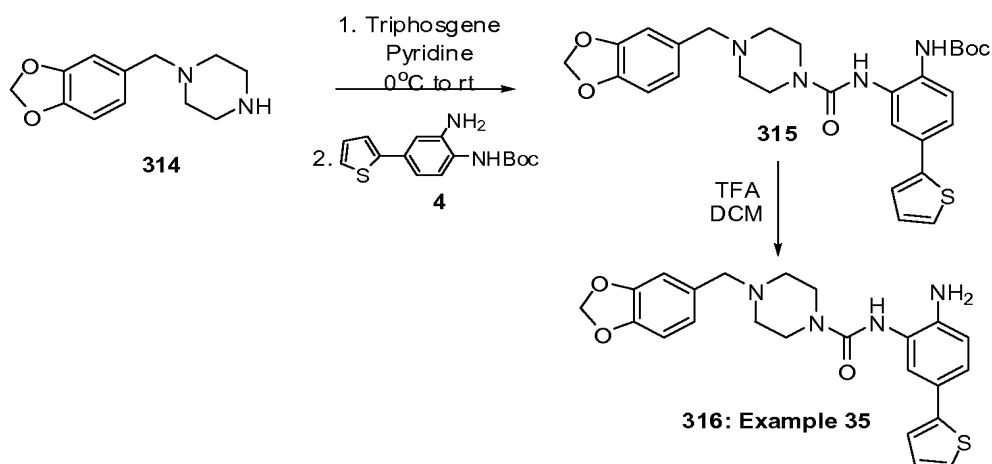
Cpd	Ex	R <sub>1</sub>	R <sub>2</sub>	X	Name	Characterization
<b>301</b>	<b>34c</b>	OAc		NH <sub>2</sub>	4-(2-amino-5-(thiophen-3-yl)phenylcarbamoyl)phenyl acetate	$^1\text{H}$ NMR (DMSO- $d_6$ ) $\delta$ (ppm): 9.77 (s, 1H), 8.05 (d, $J$ = 8.6 Hz, 2H), 7.59 to 7.55 (m, 2H), 7.51 (d, $J$ = 2.0 Hz, 1H), 7.42 (dd, $J$ = 4.9, 1.4 Hz, 1H), 7.37 (dd, $J$ = 8.2, 2.2 Hz, 1H), 7.28 (d, $J$ = 8.6 Hz, 2H), 6.81 (d, $J$ = 8.2 Hz, 1H), 5.07 (s, 2H), 2.31 (s, 3H). LRMS: 352.1 (calc) 353.0 (obs).
<b>302</b>	<b>34d</b>	OH		NH <sub>2</sub>	N-(2-amino-5-(thiophen-3-yl)phenyl)-4-hydroxybenzamide	$^1\text{H}$ NMR (DMSO- $d_6$ ) $\delta$ (ppm): 9.54 (s, 1H), 7.88 (d, $J$ = 8.6 Hz, 2H), 7.58 to 7.55 (m, 2H), 7.49 (d, $J$ = 2.2 Hz, 1H), 7.42 (dd, $J$ = 4.7, 1.4 Hz, 1H), 7.34 (dd, $J$ = 8.2, 2.7 Hz, 1H), 6.85 (d, $J$ = 8.8 Hz, 2H), 6.80 (d, $J$ = 8.2 Hz, 1H), 4.99 (s, 2H). LRMS: 310.1 (calc) 311.0 (obs).
<b>303</b>	<b>34e</b>	OH		NH <sub>2</sub>	N-(2-amino-5-(6-chloropyridin-3-yl)phenyl)-4-hydroxybenzamide	$^1\text{H}$ NMR (DMSO- $d_6$ ) $\delta$ (ppm): 10.09 (s, 1H), 9.57 (s, 1H), 8.60 (s, 1H), 8.00 (dd, $J$ =8.4, 2.5 Hz, 1H), 7.84 (d, $J$ =8.0 Hz, 2H), 7.57 (s, 1H), 7.49 (d, $J$ =8.1 Hz, 1H), 7.39 (d, $J$ =7.2 Hz, 1H), 6.84 (m, 3H), 5.11 (s, 2H). LRMS: 339.08 (calc) 339.9 (obs).
<b>304</b>	<b>34f</b>	OAc		NH <sub>2</sub>	4-(2-amino-5-(6-fluoropyridin-3-yl)phenylcarbamoyl)phenyl acetate	$^1\text{H}$ NMR (CD <sub>3</sub> OD) $\delta$ (ppm): 8.38 (s, 1H), 8.13 (m, 1H), 8.07 (d, $J$ =8.1 Hz, 2H), 7.50 (s, 1H), 7.38 (dd, $J$ =8.1, 2.1 Hz, 1H), 7.27 (d, $J$ =8.0 Hz, 2H), 7.11 (m, 1H), 6.97 (d, $J$ =8.1 Hz, 1H), 2.32 (s, 3H). LRMS: 365.36 (calc) 366.0 (obs).
<b>305</b>	<b>34g</b>	OH		NH <sub>2</sub>	N-(2-amino-5-(6-fluoropyridin-3-yl)phenyl)-4-hydroxybenzamide	$^1\text{H}$ NMR (CD <sub>3</sub> OD) $\delta$ (ppm): 8.36 (s, 1H), 8.11 (m, 1H), 7.89 (d, $J$ =8.1 Hz, 2H), 7.43 (s, 1H), 7.34 (dd, $J$ =8.0, 2.1 Hz, 1H), 7.09 (dd, $J$ =8.1, 1.9 Hz, 1H), 6.97 (d, $J$ =8.1 Hz, 1H), 6.87 (d, $J$ =8.1 Hz, 2H). LRMS: 323.32(calc) 324.0 (obs).

Cpd	Ex	R <sub>1</sub>	R <sub>2</sub>	X	Name	Characterization
306	34h	OAc		NH <sub>2</sub>	4-(4-amino-3',4'-dichlorobiphenyl-3-ylcarbamoyl)phenyl acetate	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 7.98 (d, J=8.1 Hz, 2H), 7.61 (s, 1H), 7.38 (m, 3H), 7.27 (dd, J=8.1, 3.2 Hz, 1H), 7.18 (d, J=8.1 Hz, 2H), 6.88 (d, J=8.2 Hz, 1H), 2.21 (s, 3H). LRMS: 415.27 (calc) 416.9 (obs).
307	34i	OH		NH <sub>2</sub>	N-(4-amino-4',5'-dichlorobiphenyl-3-yl)-4-hydroxybenzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.11 (s, 1H), 9.50 (s, 1H), 7.88 (d, J= 8.0 Hz, 2H), 7.75 (s, 1H), 7.62 (d, J=8.1 Hz, 1H), 7.52 (m, 2H), 7.32 (m, 1H), 6.82 (d, J= 8.1 Hz, 3H), 5.21 (s, 2H). LRMS: 373.23 (calc) 374.9 (obs).
308	34j	OH		NH <sub>2</sub>	N-(2-amino-5-(pyridin-3-yl)phenyl)-4-hydroxybenzamide	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 8.65 (s, 1H), 8.32 (d, J=6.2 Hz, 1H), 7.92 (m, 1H), 7.81 (d, J=8.0 Hz, 2H), 7.41 (s, 1H), 7.33 (m, 2H), 6.90 (d, J=8.0 Hz, 1H), 6.79 (d, J=8.0 Hz, 2H). LRMS: 305.33 (calc) 306.0 (obs).
309	34k	OH		NH <sub>2</sub>	N-(4-aminobiphenyl-3-yl)-4-hydroxybenzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.11 (s, 1H), 9.52 (s, 1H), 7.89 (d, J=8.1 Hz, 2H), 7.52 (d, J=8.2 Hz, 2H), 7.49 (s, 1H), 7.39 (m, 2H), 7.31 (m, 1H), 7.22 (m, 1H), 6.84 (d, J=8.1 Hz, 3H), 5.09 (s, 2H). LRMS: 304.34 (calc) 305.0 (found)
310	34l	OH		OH	4-hydroxy-N-(2-hydroxy-5-(thiophen-2-yl)phenyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.11 (s, 1H), 9.39 (s, 1H), 8.01 (s, 1H), 7.85 (d, J=8.1 Hz, 2H), 7.42 (d, J=4.5 Hz, 1H), 7.31 (m, 2H), 7.09 (m, 1H), 6.91 (d, J=8.2 Hz, 1H), 6.85 (d, J=8.1 Hz, 2H), 4.11 (s, 1H). LRMS: 331.36 (calc) 312.0 (found)

### Example 35

***N*-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazine-1-carboxamide (316)**

## Scheme 35



Step 1. *tert*-Butyl 2-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazine-1-carboxamido)-4-(thiophen-2-yl)phenylcarbamate (315)

[0936] A solution of triphosgene (544 mg, 1.83 mmol, 1.05 eq.) in DCM (5 mL) stirred at 0 °C under nitrogen was treated with a solution of 1-(benzo[d][1,3]dioxol-5-ylmethyl)piperazine (314, 1.16g, 5.24 mmol) in anhydrous pyridine (7 mL), added drpwise over 5 min. The resulting mixture was stirred at 0 °C for 3 h and then at room temperature for 30 min, transferred with a syringe into a flask containing solid amine 4 (832 mg, 2.87 mmol), stirred at room temperature for 21 h, diluted with DCM, washed (saturated NaHCO<sub>3</sub> then water), dried over MgSO<sub>4</sub>, filtered and concentrated. Purification by flash column chromatography (elution with 5% isopropyl alcohol in DCM) gave title compound 315 (165 mg, 11% yield) as a yellow solid.

[0937] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 8.60 (s, 1H), 8.30 (s, 1H), 7.59 (d, J = 2.2 Hz, 1H), 7.51 (dd, J = 1.0, 5.0 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.40 (dd, J = 1.0, 3.5 Hz, 1H), 7.39 (dd, J = 2.2, 8.5 Hz, 1H), 7.11 (dd, J = 3.5, 5.0 Hz, 1H), 6.88 (d, J = 1.4 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.76 (dd, J = 1.4, 7.8 Hz, 1H), 5.99 (s, 2H), 3.45 (t, J = 4.6 Hz, 1H), 3.43 (s, 2H), 2.38 (t, J = 4.6 Hz, 1H), 1.46 (s, 9H). LRMS: (calc.) 536.2; (obt.) 537.1 (MH)<sup>+</sup>.

Step 2, *N*-(2-Amino-5-(thiophen-2-yl)phenyl) -4-(benzo[d][1,3]dioxol-5-ylmethyl) piperazine-1-carboxamide (316)

[0938] A solution of compound 315 (165 mg, 0.31 mmol) in a mixture DCM - trifluoroacetic acid (3 mL, 2:1 ratio) was stirred at room temperature for 1.5 h; diluted with DCM and washed with a solution of KOH (830 mg, 15 mmol) in brine (15 mL), then brine, dried over MgSO<sub>4</sub>,



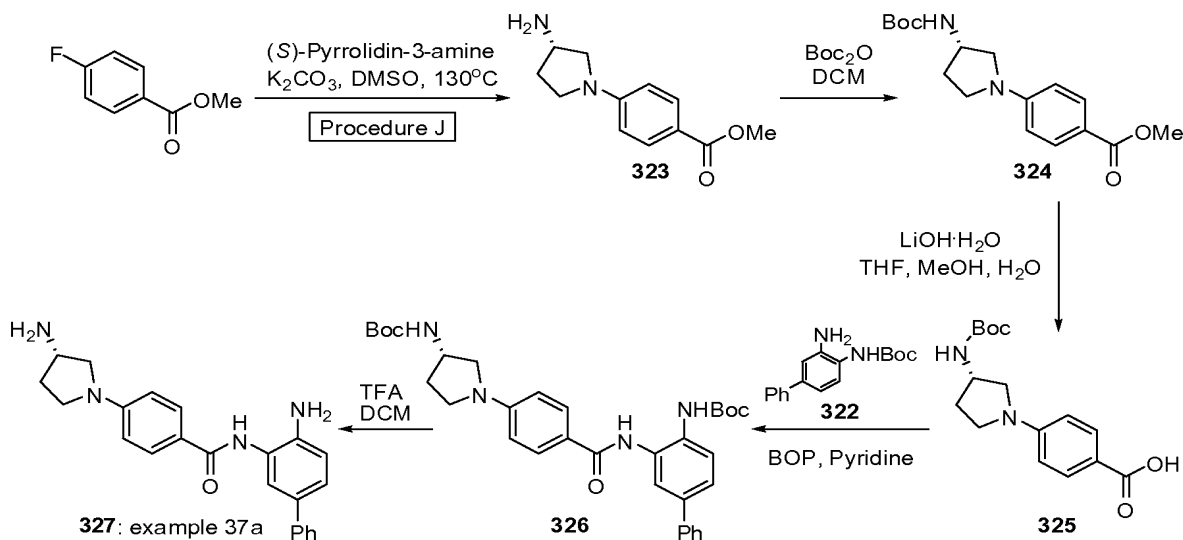
filtered and concentrated. Purification by flash column chromatography (elution with 5% to 10% MeOH in DCM) gave title compound **316** (87 mg, 0.20 mmol, 64% yield) as a pale yellow solid.

[0939]  $^1\text{H}$  NMR: (DMSO- $d_6$ )  $\delta$  (ppm): 7.92 (s, 1H), 7.33 (dd,  $J$  = 1.2, 5.1 Hz, 1H), 7.26 (d,  $J$  = 2.1 Hz, 1H), 7.21-7.18 (m, 2H), 7.03 (dd,  $J$  = 3.5, 5.1 Hz, 1H), 6.88 (d,  $J$  = 1.5 Hz, 1H), 6.85 (d,  $J$  = 8.0 Hz, 1H), 6.76 (dd,  $J$  = 1.5, 7.8 Hz, 1H), 6.72 (d,  $J$  = 7.8 Hz, 1H), 5.99 (s, 2H), 4.95 (bs, 2H), 3.44-3.42 (m, 6H), 2.36 (t,  $J$  = 4.7 Hz, 4H). LRMS: (calc.) 436.2; (obt.) 437.0 ( $\text{M}+\text{H}$ ) $^+$ .

### Example 37a

#### (S)-N-(4-Aminobiphenyl-3-yl)-4-(3-aminopyrrolidin-1-yl)benzamide (327)

#### Scheme 37



#### Step 1: (S)-Methyl 4-(3-aminopyrrolidin-1-yl)benzoate (323)

[0940]  $\text{K}_2\text{CO}_3$  (7.71 g, 55.84 mmol) was added to a solution of (S)-pyrrolidin-3-amine (5.0 g, 58.04 mmol) and methyl 4-fluorobenzoate (8.6 g, 55.81 mmol) in DMSO (20 mL). The reaction mixture was stirred for 18 h at  $130^\circ\text{C}$  in a sealed tube. The reaction mixture was cooled, diluted with AcOEt and  $\text{H}_2\text{O}$ , and extracted with AcOEt (3 times). The extract was washed with water,  $\text{NH}_4\text{Cl}$  and brine, dried over  $\text{MgSO}_4$ , filtered and concentrated to give the title compound **323** (7.98 g, 65% yield) as a pink solid.

[0941]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 7.75 (d,  $J$  = 9.0 Hz, 2H), 6.52 (d,  $J$  = 9.0 Hz, 2H), 3.74 (s, 3H), 3.60-3.55 (m, 1H), 3.45-3.41 (m, 2H), 3.32-3.25 (m, 1H), 2.97-2.93 (m, 1H), 2.09-2.01 (m, 1H), 1.72-1.68 (m, 1H). LRMS calc. 220.1; found 221.1 ( $\text{MH}$ ) $^+$ .

Step 2: (S)-Methyl 4-(3-(tert-butoxycarbonylamino)pyrrolidin-1-yl)benzoate (324)

[0942] A solution of compound **323** (2.00 g, 9.08 mmol) and  $\text{Boc}_2\text{O}$  (2.18 g, 9.99 mmol) in DCM (20 mL) was stirred at room temperature for 18 h. The reaction mixture was concentrated and the residue was purified by flash chromatography (1-2% MeOH in DCM) to give the title compound **324** (2.66 g, 91% yield) as a beige solid.

[0943]  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  (ppm): 7.75 (d,  $J = 8.8$  Hz, 2H), 7.25 (d,  $J = 6.7$  Hz, 1H), 6.54 (d,  $J = 8.8$  Hz, 2H), 4.16-4.11 (m, 1H), 3.75 (s, 3H), 3.53-3.49 (m, 1H), 3.46-3.40 (m, 1H), 3.32-3.28 (m, 1H), 3.13-3.09 (m, 1H), 2.17-2.10 (m, 1H), 1.94-1.87 (m, 1H). LRMS calc. 320.2; found 321.1 (MH)+.

Step 3: (S)-4-(3-(tert-Butoxycarbonylamino)pyrrolidin-1-yl)benzoic acid (325)

[0944]  $\text{LiOH}\cdot\text{H}_2\text{O}$  (1.14 g, 27.26 mmol) and water (5 mL) was added to a solution of **324** (4.36 g, 13.62 mmol) in THF (15 mL) and MeOH (15 mL). The reaction mixture was stirred at room temperature for 22 h, diluted with water and acidified with HCl (pH 4-5). The precipitate obtained was collected by filtration and rinsed with water to give the title compound **325** (3.91 g, 94% yield) as a white solid.

[0945] LRMS calc. 306.2; found 307.1 (MH)+.

Step 4: (S)-tert-Butyl 3-(4-(3-tert-butoxycarbonylamino)pyrrolidin-1-yl)benzamido)biphenyl-4-ylcarbamate (326)

[0946] The acid **325** (3.23 g, 7.03 mmol) and BOP (4.66 g, 10.55 mmol) were added to a solution of **322** (1.2 g, 7.03 mmol) (Compound **322** was synthesized following general procedures **B** and **C** starting from compound **2** and phenylboronic acid) in pyridine (40 mL). The reaction mixture was stirred at room temperature for 24 h, concentrated under reduced pressure, diluted with DCM, washed with water,  $\text{NaHCO}_3$  and brine. The residue was purified by flash chromatography (2-4% MeOH in DCM) to give the title compound **326** (1.74 g, 43%) as a brown solid.

[0947] LRMS calc. 572.3; found 573.1 (MH)+.

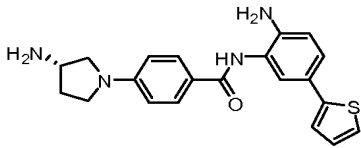
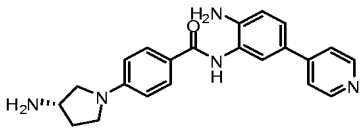
Step 5: (S)-N-(4-Aminobiphenyl-3-yl)-4-(3-aminopyrrolidin-1-yl)benzamide (327)

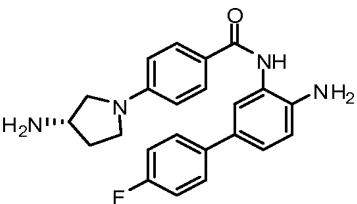
[0948] TFA (1 mL) was added to a solution of **326** (370 mg, 0.65 mmol) in DCM (1 mL). The reaction mixture was stirred at room temperature for 24 h, concentrated and the residue was partitioned between EtOAc and  $\text{NaHCO}_3$ . The aqueous layer was extracted with fresh EtOAc and the combined organic layers were washed with brine, dried over  $\text{MgSO}_4$  and concentrated. The

residue was purified using the Biotage system, (cartridge Biotage Si 25+M, ), eluent MeOH/DCM (10% to 40%) to afford the title compound **327** (161 mg, 67% yield).

[0949]  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  (ppm): 7.90 (d,  $J=8.8$  Hz, 2H), 7.56 (d,  $J=7.8$  Hz, 2H), 7.46 (d,  $J=2.2$  Hz, 1H), 7.37 (t,  $J=7.6$  Hz, 2H), 7.35 (dd,  $J=10.4$ , 2.3 Hz, 1H), 7.24 (t,  $J=7.2$  Hz, 1H), 6.97 (d,  $J=8.4$  Hz, 1H), 6.65 (d,  $J=8.8$  Hz, 2H), 3.76 (quint,  $J=5.3$  Hz, 1H), 3.61 (dd,  $J=10.4$ , 6.3 Hz, 1H), 3.61-3.54 (m, 1H), 3.45-3.39 (m, 1H), 3.20 (dd,  $J=10.2$ , 4.5 Hz, 1H), 2.31 (sext,  $J=6.7$  Hz, 1H), 1.94 (sext,  $J=7.3$  Hz, 1H). LRMS calc. 372.5; found 373.2 (MH) $^+$ .

Table 18: Characterization of compounds prepared according to Scheme 37.

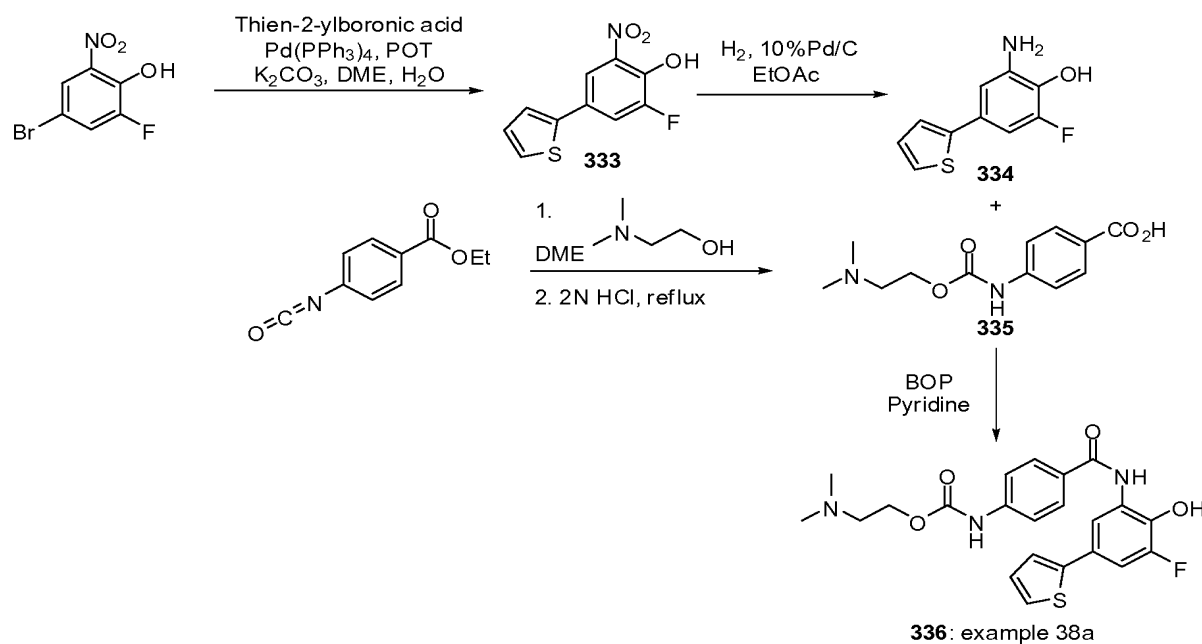
Cpd	Ex	Structure	Name	Characterization
328	37b		(S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(3-aminopyrrolidin-1-yl)benzamide	$^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ) $\delta$ (ppm): 9.42 (s, 1H), 7.88 (d, $J=8.8$ Hz, 2H), 7.46 (d, $J=2.2$ Hz, 1H), 7.36 (dd, $J=5.1$ , 1.0 Hz, 1H), 7.27 (dd, $J=8.4$ , 2.2 Hz, 1H), 7.25 (dd, $J=3.5$ , 1.0 Hz, 1H), 7.05 (dd, $J=5.1$ , 3.7 Hz, 1H), 6.81 (d, $J=8.4$ Hz, 1H), 6.55 (d, $J=9.0$ Hz, 2H), 5.08 (s, 2H), 3.64 (quint, $J=5.4$ Hz, 1H), 3.49-3.42 (m, 2H), 3.3 (m, 1H, overlap with $\text{DMSO}-d_6$ ), 3.00 (dd, $J=9.8$ , 4.5 Hz, 1H), 2.15-2.07 (m, 1H), 1.80-1.73 (m, 1H). LRMS: 378.2 (calc) 379.0(found).
329	37c		(S)-N-(2-amino-5-(pyridin-4-yl)phenyl)-4-(3-aminopyrrolidin-1-yl)benzamide	$^1\text{H}$ NMR ( $\text{CD}_3\text{OD}$ ) $\delta$ (ppm): 8.46 (d, $J=6.5$ Hz, 2H), 7.89 (d, $J=9.0$ Hz, 2H), 7.64 (d, $J=6.5$ Hz, 2H), 7.63 (d, $J=2.3$ Hz, 1H), 7.51 (dd, $J=8.4$ , 2.3 Hz, 1H), 6.98 (d, $J=8.4$ Hz, 1H), 6.62 (d, $J=9.0$ Hz, 2H), 3.68 (quint, $J=5.3$ Hz, 1H), 3.58 (dd, $J=10.0$ , 6.3 Hz, 1H), 3.57-3.52 (m, 1H), 3.42-3.35 (m, 1H), 3.12 (dd, $J=9.8$ , 4.9 Hz, 1H), 2.25 (sext, $J=4.9$ Hz, 1H), 1.89 (sext, $J=6.1$ Hz, 1H). LRMS: (calc.) 373.45 (found) 374.3 (MH) $^+$

Cpd	Ex	Structure	Name	Characterization
330	37d		(S)-N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(3-aminopyrrolidin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.42 (s, 1H), 7.87 (d, J=8.8 Hz, 2H), 7.56 (dd, J=9.0, 5.7 Hz, 2H), 7.47 (d, J=2.2 Hz, 1H), 7.25 (dd, J=8.2, 2.0 Hz, 1H), 7.20 (t, J=8.8 Hz, 2H), 6.84 (d, J=8.2 Hz, 1H), 6.54 (d, J=8.8 Hz, 2H), 5.01 (d, J=10.0 Hz, 1H), 3.64 (quint, J=5.5 Hz, 1H), 3.47 (dd, J=10.2, 6.3 Hz, 1H), 3.46-3.40 (m, 1H), 3.36-3.29 (m, 1H), 3.01 (dd, J=10.0, 4.3 Hz, 1H), 2.10 (sext, J=6.3 Hz, 1H), 1.78 (sext, J=7.0 Hz, 1H) LRMS: (calc.) 390.45 (found) 391.2 (MH) <sup>+</sup>

## Example 38a

## 2-(Dimethylamino)ethyl 4-(2-hydroxy-5-(thiophen-2-yl)pyridin-3-ylcarbamoyl)phenylcarbamate (336)

## Scheme 38



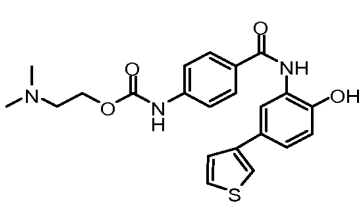
## Steps 1-2: 3-Amino-5-(thiophen-2-yl)pyridin-2-ol (334)

[0950] Following the same procedure as described in Example 1, steps 2 and 3 (scheme 1), but substituting compound 2 by 4-bromo-2-fluoro-6-nitrophenol, the title compound 334 was obtained as a beige solid (step 1: 53%, step 2: 43%). LRMS: (calc.) 209.0, (obt.) 210.3 (MH)<sup>+</sup>.

Steps 3-4: 2-(Dimethylamino)ethyl 4-(2-hydroxy-5-(thiophen-2-yl)pyridin-3-ylcarbamoyl)-phenylcarbamate (336)

**[0951]** Following the same procedure as described in Example 33a, steps 1 and 2 (scheme 33), but substituting pyridine-3-yl-methanol by 2-(dimethylamino)ethanol and compound **4** by compound **334**, the title compound **336** was obtained as a white solid (step 4: 14 mg, 5% yield). <sup>1</sup>H NMR. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 10.1 (s, 1H), 9.82 (s, 1H), 8.22 (s, 1H), 7.92 (b s, 1.0 Hz, 2H), 7.75 (bs, 1H), 7.62 (m, 2H), 7.49 (bs, 1H), 7.40 (m, 2H), 7.11 (s, 1H), 4.21 (m, 2H), 2.58 (m, 2H), 2.22 (s, 6H). LRMS: (calc.) 443.1, (obt.) 444.2 (MH)<sup>+</sup>.

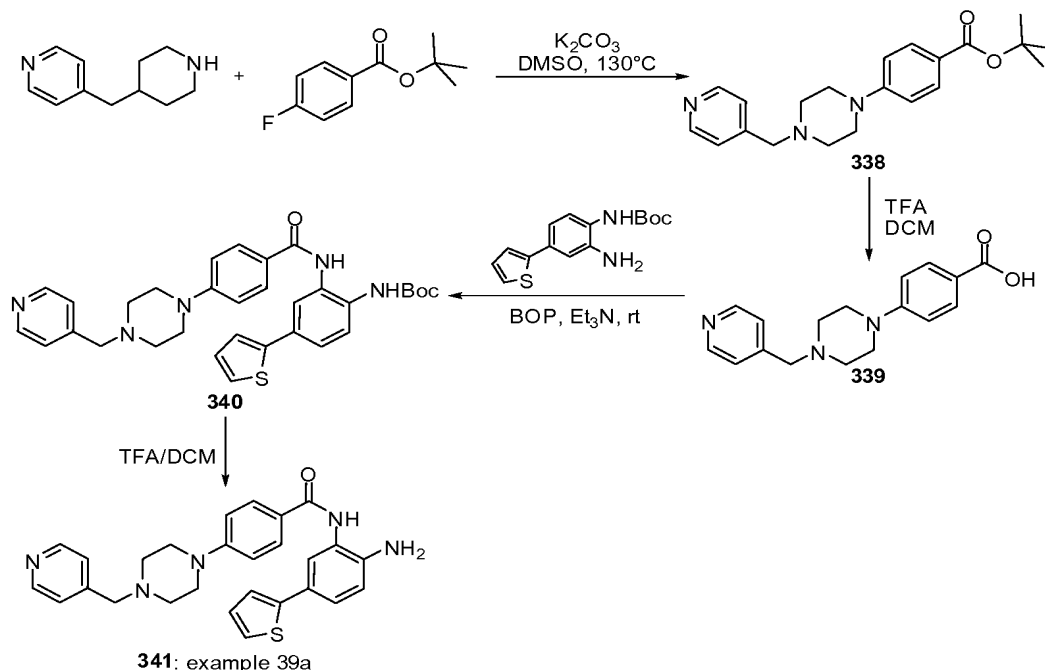
Table 19: Characterization of compounds prepared according to Scheme 38

Cpd	Ex	Structure	Name	Characterization
337	38b		2-(dimethylamino)ethyl 4-(2-hydroxy-5-(thiophen-3-yl)phenylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.11 (s, 1H), 9.58 (s, 1H), 7.98 (s, 1H), 7.92 (d, J=8.7 Hz, 2H), 7.61 (m, 4H), 7.42 (d, J=6.8 Hz, 1H), 7.38 (d, J=8.4 Hz, 1H), 6.95 (d, J=8.7 Hz, 1H), 4.20 (t, J=5.3 Hz, 2H), 2.51 (t, J=5.3 Hz, 2H), 2.19 (s, 6H). LRMS: 425.51 (calc) 426.1 (found)

**Example 39a**

**N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(4-(pyridin-4-ylmethyl)piperazin-1-yl)benzamide (341)**

Scheme 39



Step1: tert-Butyl 4-(4-(pyridin-4-ylmethyl)piperazin-1-yl)benzoate (338)

[0952] To a solution of 1-[(4-Pyridyl)methyl] piperazine (1.00 g, 5.6 mmol) in DMSO (4.5 mL) in a pressure vessel was added *t*-butyl-4-fluorobenzoate (1.05 g, 5.4 mmol) followed by potassium carbonate (0.74 g, 5.4 mmol). The pressure vessel was closed and the mixture was stirred at 130 °C for 21 h. The mixture was diluted with EtOAc (300 mL) and water (50 mL). The organic layer was separated, washed with a saturated NaHCO<sub>3</sub> solution, brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue obtained was purified by flash chromatography using 0-5% MeOH in DCM to afford the title compound **338** as a pink solid (1.34 g, 71% yield).

[0953] LRMS: (calc.) 353.2, (obt.) 354.3 (MH)<sup>+</sup>.

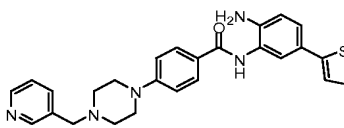
Steps 2-4: N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(4-(pyridin-4-ylmethyl)piperazin-1-yl)benzamide (341)

[0954] Following the same procedure as described in Example 2a, steps 3-5 (scheme 2), but substituting compound **39** by compound **338**, the title compound **341** was obtained as a beige solid (0.105 g, 62%).

[0955] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) □(ppm): 9.50 (s, 1H), 8.53 (dd, J = 4.4, 1.6 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 6.0 Hz, 2H), 7.35 (dd, J = 5.2, 1.2 Hz, 1H), 7.28 (dd, J = 8.2, 2.2 Hz, 1H), 7.24 (dd, J = 3.6, 1.2 Hz, 1H), 7.05 (dd, J = 5.2, 3.6 Hz, 1H), 7.01

(d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.0 Hz, 1H), 5.10 (s, 2H), 3.58 (s, 2H), 3.32 (bt, J = 5.2 Hz, 4H), 2.54 (bt, J = 5.0 Hz, 4H). LRMS: (calc.) 469.2, (obt.) 470.2 (MH)<sup>+</sup>.

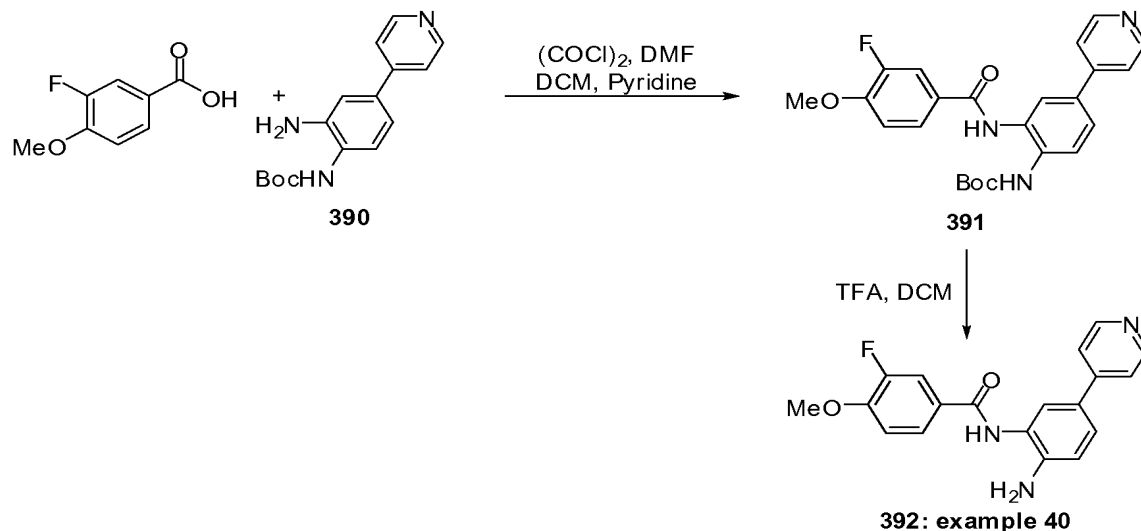
Table 20: Characterization of compounds prepared according to Scheme 39.

Cpd	Ex	Structure	Name	Characterization
342	39b		N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-(pyridin-3-ylmethyl)piperazin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.48 (s, 1H), 8.52 (d, J=1.6 Hz, 1H), 8.47 (dd, J=4.9, 1.8 Hz, 1H), 7.87 (d, J=9.0 Hz, 2H), 7.74 (dt, J=8.0, 1.8 Hz, 1H), 7.44 (d, J=2.3 Hz, 1H), 7.37 (ddd, J= 7.6, 4.9, 0.8 Hz, 1H), 7.34 (dd, J=5.1, 1.2 Hz, 1H), 7.26 (dd, J=8.4, 2.2 Hz, 1H), 7.22 (dd, J=3.5, 1.2 Hz, 1H), 7.03 (dd, J=5.1, 3.5 Hz, 1H), 6.98 (d, J=9.0 Hz, 2H), 6.79 (d, J=8.4 Hz, 1H), 5.08 (s, 2H), 3.56 (s, 2H), 3.31-3.27 (m, 4H), 2.52-2.48 (m, 4H). LRMS: (calc.) 469.60 (found) 470.3 (MH) <sup>+</sup>

### Example 40

#### N-(2-Amino-5-(pyridin-4-yl)phenyl)-3-fluoro-4-methoxybenzamide (392)

#### Scheme 40



#### Step1: tert-Butyl 2-(3-fluoro-4-methoxybenzamido)-4-(pyridin-4-yl)phenylcarbamate (391)

[0956] To a suspension of 3-fluoro-4-methoxybenzoic acid (125 mg, 0.736 mmol) in DCM (10 mL), oxalyl chloride (0.442 mL, 0.883 mmol) and DMF (2 drops) were added. The reaction was stirred at room temperature for 30 min and a solution was obtained. A solution of compound 390 (210 mg, 0.736 mmol) (390 was synthesized following general procedures B and C starting

from compound **2** and pyridin-4-ylboronic acid) in pyridine (10 mL) was added and the reaction was stirred for an additional hour, quenched with water, dissolved in AcOEt and washed with water. The organic layer was separated and dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum. The residue was purified via Isco (12 g column, 40-100% EtOAc/hexanes solvent gradient) to give the title compound **391** as a light yellowed (60 mg, 18% yield).

[0957] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm) 1H: 9.88 (s, 1H), 8.84 (s, 1H), 8.61 (dd, J=4.5, 1.6 Hz, 2H), 7.94-7.91 (m, 1H), 7.85-7.81 (m, 2H), 7.78-7.75 (m, 1H), 7.68-7.65 (m, 3H), 7.34 (t, J=8.6 Hz, 1H), 3.92 (s, 3H), 1.45 (s, 9H).

Step 2. N-(2-Amino-5-(pyridin-4-yl)phenyl)-3-fluoro-4-methoxybenzamide (392)

[0958] Following the general procedure **G**, the title compound was obtained as a yellow solid (25 mg, 27% yield).

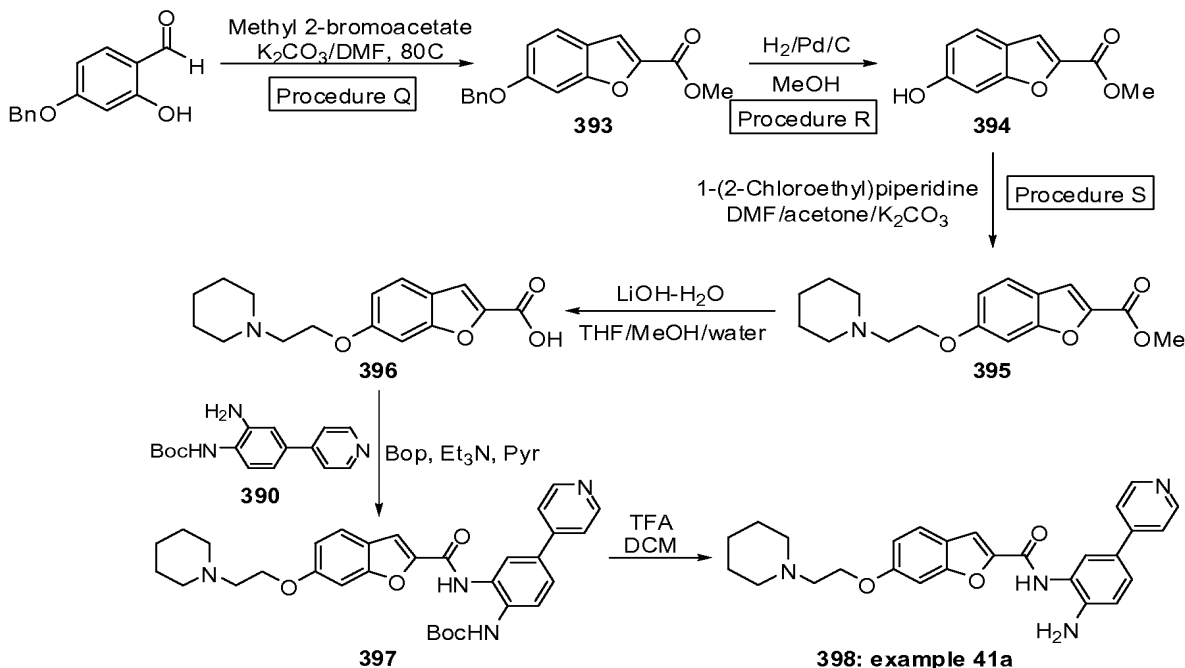
[0959] <sup>1</sup>H NMR (MeOD-d<sub>4</sub>) δ (ppm) 1H: 8.45 (d, J=4.7 Hz, 2H), 7.85 - 7.76 (m, 2H), 7.65 - 7.63 (m, 3H), 7.53 (dd, J=8.5, 2.3 Hz, 1H), 7.20 (t, J=8.6 Hz, 1H), 6.97 (d, J=8.6 Hz, 1H), 3.95 (s, 3H). LRMS: (calc.) 337.1 (found) 338.2 (MH)+.

**Example 41a**

**N-(2-amino-5-(pyridin-4-yl)phenyl)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-2-carboxamide (398)**



## Scheme 41

Step 1. Methyl 6-(benzyloxy)benzofuran-2-carboxylate (393)

[0960] To a stirred solution of 4-(benzyloxy)-2-hydroxybenzaldehyde (10 g, 43.9 mmol) in DMF (60 mL), was added methyl bromoacetate (48.3 mmol, 4.57 mL), and potassium carbonate (24.2 g, 175.6 mmol). The solution was heated to 80 °C and stirred for 16 h. The reaction was quenched with water (100 mL) and aqueous extraction was performed with AcOEt (2 x 50 mL). The organic phase was dried with sodium sulfate and concentrated. Purification was achieved via silica gel chromatography employing 0-30% AcOEt in hexane gradient. This afforded **393** as a light yellow solid (4.5 g, 37%).

[0961]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 7.68-7.64 (m, 2H), 7.49-7.45 (m, 2H), 7.42-7.31 (m, 4H), 7.07-7.04 (m, 1H), 5.18 (s, 2H), 3.85 (s, 2H).

Step 2. Methyl 6-hydroxybenzofuran-2-carboxylate (394)

[0962] To a stirred solution of **393** (1.2 g, 4.26 mmol) in MeOH (20 mL) was added palladium on charcoal (250 mg). The flask was purged with hydrogen gas for 1 minute and then the reaction was stirred under a hydrogen atmosphere for 15 hours. The palladium was filtered off through Celite and the filtrate was evaporated via rotary evaporation, and the resulting solid dried under vacuum to afford **394** as a white solid (700 mg, 86%).

[0963] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 10.07 (s, 1H), 7.63 (s, 1H), 7.56 (d, J=8.0 Hz, 1H), 6.98 (s, 1H), 6.84 (d, J=9.0 Hz, 1H), 3.84 (s, 3H).

Step 3. Methyl 6-(2-(piperidin-1-yl)ethoxy)benzofuran-2-carboxylate (395)

[0964] A solution of **394** (350 mg, 1.82 mmol), 1-(2-Chloroethyl)piperidine (269 mg, 1.82 mmol) and K<sub>2</sub>CO<sub>3</sub> (503 mg, 3.64 mmol) in DMF (10 mL) and acetone (10 mL) was stirred at 60 °C for 3 h and then at room temperature for 3 days (or until completion). The crude product was dissolved in AcOEt and washed with water. The organic layer was separated and dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum. The residue was purified via Isco (0-25% MeOH/EtOAc) to afford the title compound **395** as a white solid (330 mg, 60% yield).

[0965] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 7.68-7.62 (m, 2H), 7.31 (d, J=1.8 Hz, 1H), 6.97 (dd, J=8.8, 2.3 Hz, 1H), 4.12 (t, J=5.9 Hz, 2H), 3.85 (s, 3H), 2.66 (t, J=5.9 Hz, 2H), 2.47-2.40 (m, 4H), 1.48 (quintet, J=5.5 Hz, 4H), 1.39-1.35 (m, 2H).

Steps 4-6. N-(2-Amino-5-(pyridin-4-yl)phenyl)-6-(2-(piperidin-1-yl)ethoxy)benzofuran-2-carboxamide (398)

[0966] Following the general procedures **P**, **G** and **F**, the title compound was obtained as a yellow solid (60 mg, 25% yield, last step).

[0967] <sup>1</sup>H NMR (MeOD-d<sub>4</sub>) δ (ppm): 8.44 (d, J=6.5 Hz, 2H), 7.71 (d, J=2.2 Hz, 1H), 7.62 - 7.50 (m, 5H), 7.18 (d, J=1.8 Hz, 1H), 6.97 (d, J=8.6 Hz, 2H), 4.17 (t, J=5.7 Hz, 2H), 2.80 (t, J=5.5 Hz, 2H), 2.60 - 2.50 (m, 4H), 1.63 (quintet, J=5.7 Hz, 4H), 1.50 - 1.47 (m, 2H). LRMS: (calc.) 456.2 (found) 457.2 (MH)+.

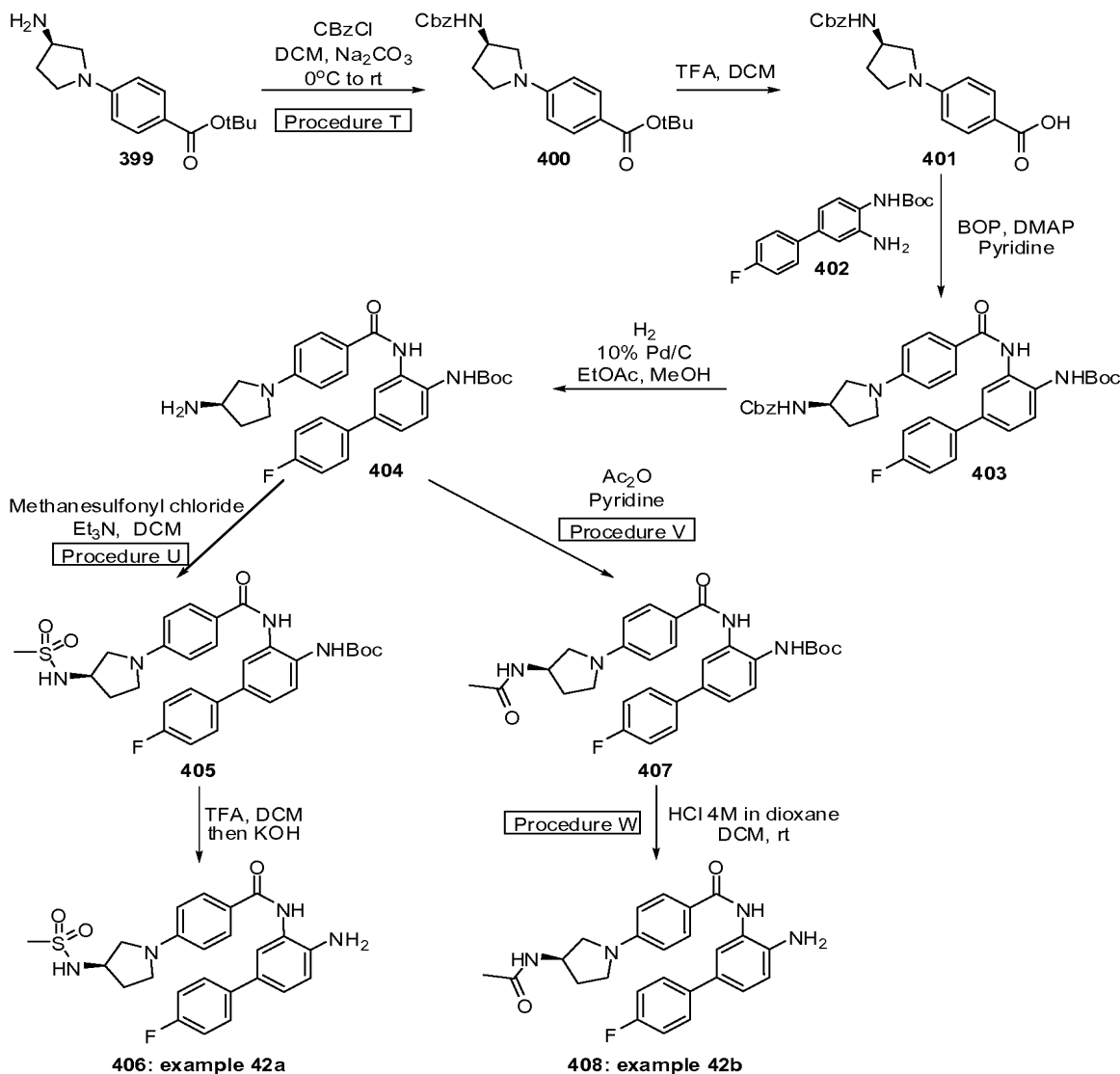
**Example 42a**

**(R)-N-(4-Amino-4'-fluorobiphenyl-3-yl)-4-(3-(methylsulfonamido)pyrrolidin-1-yl)benzamide (406)**

**Example 42b**

**(R)-4-(3-Acetamidopyrrolidin-1-yl)-N-(4-amino-4'-fluorobiphenyl-3-yl)benzamide (408)**

## Scheme 42



**Step 1: (R)-tert-Butyl 4-(3-(benzyloxycarbonylamino)pyrrolidin-1-yl)benzoate (400)**

[0968]  $\text{Na}_2\text{CO}_3$  (7.81 g, 73.7 mmol) then CbzCl (6.88 mL, 48.2 mmol) was added to a solution of **399** (10.28 g, 39.2 mmol) (**399** was synthesized following the procedure **J** starting from (R)-pyrrolidin-3-amine and tert-butyl 4-fluorobenzoate) in DCM (196 mL) at  $0^\circ\text{C}$ . The reaction mixture was slowly warmed to room temperature and stirred for 16 h. It was then quenched with saturated  $\text{NH}_4\text{Cl}$ , stirred for 30 min, diluted with DCM, washed with brine then  $\text{H}_2\text{O}$ , dried with  $\text{MgSO}_4$ , filtered and concentrated to afford the title compound **400** (16.4 g, quant.) as a beige solid.

[0969] LRMS calc. 396.2; found 397.2 (MH)<sup>+</sup>.

Steps 2-4: (R)-tert-Butyl 3-(4-(3-aminopyrrolidin-1-yl)benzamido)-4'-fluorobiphenyl-4-ylcarbamate (404)

[0970] Compound **402** was synthesized following general procedures **B** and **C** starting from compound **2** and 4-fluorophenylboronic acid. Then following the general procedures **I**, **F**, and **R**, the title compound was obtained (2.0 g, 47% yield, last step).

[0971] LRMS calc. 490.2; found 491.3 (MH)<sup>+</sup>.

Step 5a: (R)-tert-butyl 4'-fluoro-3-(4-(3-(methylsulfonamido)pyrrolidin-1-yl)benzamido)-biphenyl-4-ylcarbamate (405)

[0972] A solution of compound **404** (420 mg, 0.856 mmol) in DCM (2 mL) was cooled down to 0 °C and treated with neat methanesulfonyl chloride (148 mg, 1.29 mmol). The mixture was allowed to warm up to room temperature for 18 h. Cooled down to 0 °C, treated with sat. NaHCO<sub>3</sub> (1 mL), stirred for 1.5 h, diluted with DCM, washed with sat NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub> and concentrated under vacuum to afford the title compound **405** as a brown solid (430 mg, 88%) which was used without further purification

[0973] LRMS calc. 568.2; found 569.3 (MH)<sup>+</sup>.

Step 6a: (R)-N-(4-Amino-4'-fluorobiphenyl-3-yl)-4-(3-(methylsulfonamido)pyrrolidin-1-yl)benzamide (406)

[0974] Starting from compound **405**, the general procedure **G** was followed to give the title compound **406** as a beige powder (137 mg, 36% yield).

[0975] <sup>1</sup>HNMR: (DMSO-d<sub>6</sub>) δ (ppm): 9.44 (s, 1H), 7.89 (d, 2H), 7.59-7.56 (m, 2H), 7.48-7.47 (m, 2H), 7.27 (dd, 1H), 7.21 (m, 2H), 6.85 (d, 1H), 6.59 (d, 2H), 5.03 (s, 2H), 4.10-4.40 (m, 1H), 3.65-3.61 (m, 1H), 3.48-3.42 (m, 1H), 3.32-3.29 (m, 1H), 3.22-3.18 (m, 1H), 3.00 (s, 3H), 2.32-2.24 (m, 1H), 2.02-2.19 (m, 1H). LRMS(ESI): (calc.) 468.2 (found) 469.1 (MH)<sup>+</sup>

Step 5b: (R)-tert-Butyl 3-(4-(3-acetamidopyrrolidin-1-yl)benzamido)-4'-fluorobiphenyl-4-ylcarbamate (407)

[0976] To a solution of **404** (0.295 g, 0.601 mmol) in pyridine (3.0 mL) under nitrogen was added acetic anhydride (1.59 mL, 16.84 mmol), and the mixture was stirred for 19 h at room temperature. The solvent was evaporated and the residue obtained was evaporated twice with toluene and triturated with a mixture of Et<sub>2</sub>O and hexanes. The solid was filtered, air-dried and then dried under vacuum to afford the title compound **407** as a light pink solid (280 mg, 85%).

[0977] LRMS calc. 532.3; found 533.3 (MH)<sup>+</sup>.

Step 6b: (R)-4-(3-Acetamidopyrrolidin-1-yl)-N-(4-amino-4'-fluorobiphenyl-3-yl)benzamide (408)

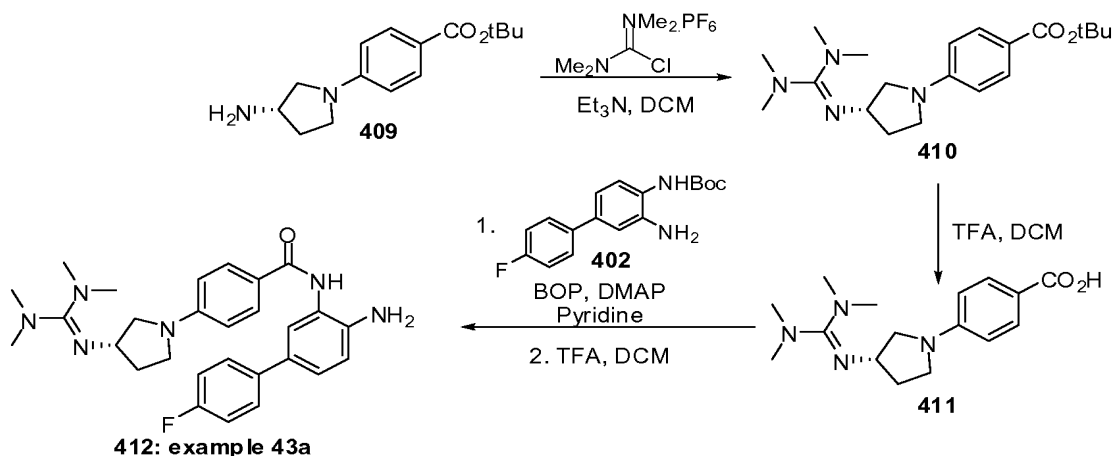
[0978] To a suspension of **407** (0.280 g, 0.526 mmol) in DCM (5 mL) and dioxane (5.0 mL) was added HCl in dioxane (2.4 mL, 9.46 mmol). The mixture was stirred for 3 h at room temperature. The solvent was evaporated and the residue obtained was triturated in Et<sub>2</sub>O, filtered and dried under vacuum. The light pink solid obtained was suspended in EtOAc, washed with sat NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub>, filtered and evaporated to afford a beige solid that was triturated overnight with Et<sub>2</sub>O. The solid was then filtered and dried under vacuum to give the title compound **408** (167 mg, 69% yield).

[0979] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.42 (s, 1H), 8.18 (d, J=6.8 Hz, 1H), 7.87 (d, J=8.8 Hz, 2H), 7.56 (dd, J=9.0, 5.4 Hz, 2H), 7.47 (d, J=2.0 Hz, 1H), 7.25 (dd, J=8.4, 2.4 Hz, 1H), 7.20 (t, J=8.8 Hz, 2H), 6.84 (d, J=8.4 Hz, 1H), 6.57 (d, J=8.8 Hz, 2H), 5.02 (s, 2H), 4.37 (sext, J=5.8 Hz, 1H), 3.54 (dd, J=10.4, 6.4 Hz, 1H), 3.43 (m, 1H), 3.36 (m, 1H), 3.12 (dd, J=10.4, 4.4 Hz, 1H), 2.17 (sext, J=6.8 Hz, 1H), 1.89 (sext, J=6.2 Hz, 1H), 1.80 (s, 3H). LRMS: calc. 432.20, found: 433.2 (MH)<sup>+</sup>.

### Example 43a

**(S)-N-(4-Amino-4'-fluorobiphenyl-3-yl)-4-(3-(bis(dimethylamino)methyleneamino)pyrrolidin-1-yl)benzamide (412)**

#### Scheme 43



Step 1. (S)-tert-Butyl 4-(3-(bis(dimethylamino)methyleneamino)pyrrolidin-1-yl)benzoate (410)

[0980] A solution of chloro N,N,N',N'-tetramethylformamidinium hexafluorophosphate (1.37 g, 4.9 mmol, 1.3 eq.), compound **409** (1.01 g, 3.9 mmol) and TEA (1.3 mL, 10 mmol) in dry DCM (10 mL), was stirred at room temperature for 1.5 h; diluted (DCM), washed with saturated NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>), filtered and concentrated to furnish title compound **410** (1.31 g, 3.6 mmol, 94% yield) as a dark foam, 91-95% pure by HPLC. Used without additional purification. Compound **409** was obtained using general procedure **J** starting from tert-butyl 4-fluorobenzoate compound with (S)-pyrrolidin-3-amine).

[0981] LRMS: (calc.) 360.3 Found: 361.3 (MH)<sup>+</sup>.

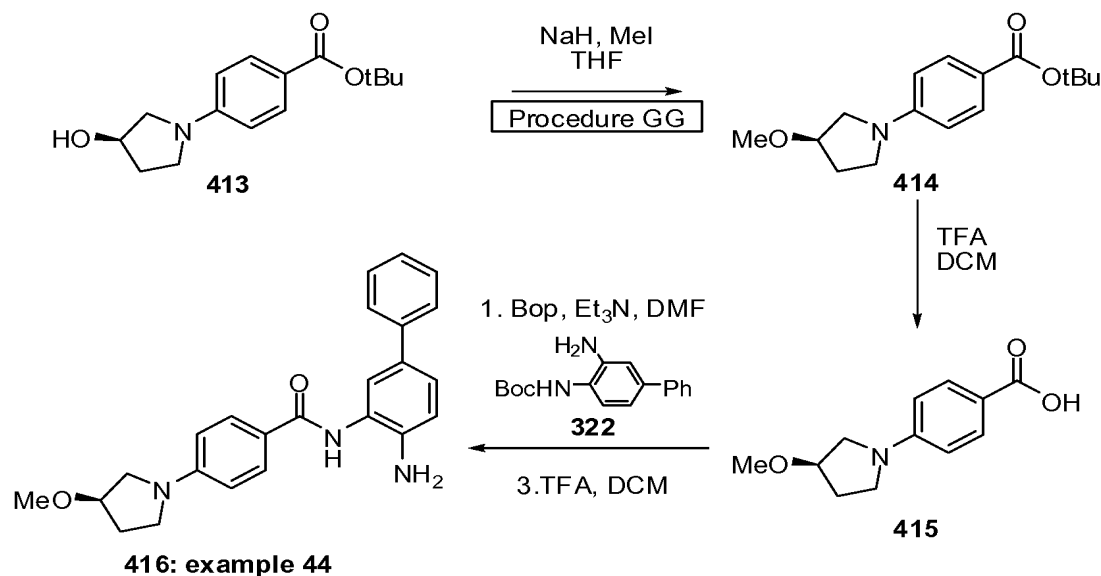
Steps 2-4 (S)-N-(4-Amino-4'-fluorobiphenyl-3-yl)-4-(3-(bis(dimethylamino)methyleneamino)pyrrolidin-1-yl)benzamide (412)

[0982] Following the general procedures **I**, **F** and **G**, the title compound **412** was obtained as an amorphous solid, formic acid salt after purification by semipreparative HPLC (3.0 mg, 6.1 umol, 8% yield, last step).

[0983] <sup>1</sup>HNMR: (DMSO-d<sub>6</sub>) δ (ppm): 9.48(s, 1H), 8.52(bs, formic acid), 7.90(d, 2H), 7.59-7.55(m, 2H), 7.47(d, 1H), 7.28(dd, 1H), 7.21(dt, 2H), 6.85(d, 1H), 6.63(d, 2H), 5.04(s, 2H), 4.23(m, 1H), 3.69(m, 1H), 3.51(m, 2H), 2.93 (bs, 12H), 2.08(m, 2H), 1.80 (bs, 1H). LRMS: (calc.) 488.4 (found) 489.4 (MH)<sup>+</sup>

**Example 44a****(R)-N-(4-Aminobiphenyl-3-yl)-4-(3-methoxypyrrolidin-1-yl)benzamide (416)**

Scheme 44



Step 1. (R)-tert-Butyl 4-(3-methoxypyrrolidin-1-yl)benzoate (**413**)

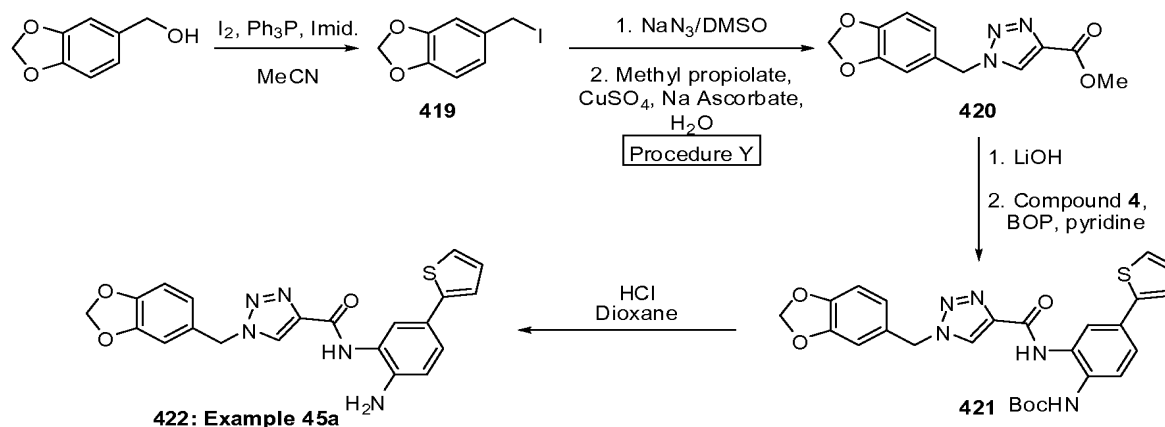
[0984] Starting from tert-butyl 4-fluorobenzoate compound and (R)-pyrrolidin-3-ol, the general procedure J was followed to afford the compound **413**. Then, NaH (0.395 g, 9.87 mmol) was added to a solution of compound **413** (2.0 g, 7.59 mmol) in THF (38 ml) at 0 °C. The mixture was stirred at 0 °C for 5 min, iodomethane (0.617 ml, 9.87 mmol) was added at 0 °C and stirred at room temperature for 18 h. The mixture was quenched with brine followed by an extraction with EtOAc (3x). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford the crude product **413** as a yellow solid (1.47 g, quantitative yield) which was used in the next step without further purification.

[0985] LRMS: (calc.) 277.2 (found) 278.3 (MH)<sup>+</sup>

Steps 2-4. (R)-N-(4-Aminobiphenyl-3-yl)-4-(3-methoxypyrrolidin-1-yl)benzamide (**416**)

[0986] Starting from **414**, the general procedures I, F (with **322**) and G were followed to afford the title compound **416** as a white solid (140 mg, 20%, last step),

[0987] <sup>1</sup>H NMR (MeOD-d<sub>4</sub>) δ (ppm): 7.90 (d, J=9.0 Hz, 2H), 7.56 (dd, J=7.2, 1.2 Hz, 2H), 7.47 (d, J=2.2 Hz, 1H), 7.37 (t, J=7.4 Hz, 2H), 7.36 (dd, J=8.0, 2.4 Hz, 1H), 7.24 (t, J=7.4 Hz, 1H), 6.97 (d, J=8.2 Hz, 1H), 6.64 (d, J=9.0 Hz, 2H), 4.14-4.0 (m, 1H), 3.54 (dd, J=11.0, 4.7 Hz, 1H), 3.48-3.40 (m, 3H), 3.38 (s, 3H), 2.28-2.10 (m, 2H). LRMS: (calc.) 387.2 (found) 388.3 (MH)<sup>+</sup>.

**Example 45a****N-(2-amino-5-(thiophen-2-yl)phenyl)-1-(benzo[d][1,3]dioxol-5-ylmethyl)-1H-1,2,3-triazole-4-carboxamide (422)****Scheme 45****Step 1. 5-(Iodomethyl)benzo[d][1,3]dioxole (419)**

**[0988]** Benzo[d][1,3]dioxol-5-ylMeOH (1.0 g, 6.57 mmol) was added in a single portion to a solution of the iodine (2.00 g, 7.89 mmol), imidazole (537 mg, 7.89 mmol) and PPh<sub>3</sub> (2.07 g, 7.89 mmol) in MeCN (10 mL) at 0 °C. The reaction was stirred for 1 h and quenched by pouring into a saturated solution of sodium thiosulfate. The product was extracted with AcOEt, washed with brine, dried with MgSO<sub>4</sub> and filtered. Solvent was removed under vacuum and the yellow solid residue was suspended in 25% AcOEt in hexanes and filtered through a silica plug. The filtrate was concentrated to afford the title compound **419** (1.70 g, 99% yield) and was used without further purification.

**[0989]** LRMS: (calc.) 262.0 (found) 134.9 (M-I)+.

**Step 2. Methyl 1-(benzo[d][1,3]dioxol-5-ylmethyl)-1H-1,2,3-triazole-4-carboxylate (420)**

**[0990]** Compound **419** (1.72 g, 6.57 mmol) was dissolved in a 0.5 M solution of sodium azide (13.1 mL, 6.57 mmol) in DMSO (2 mL), stirred at room temperature overnight and quenched by pouring into a saturated solution of sodium thiosulfate. The compound was extracted with AcOEt, washed with brine, dried over MgSO<sub>4</sub> and filtered to give a yellow solution. Water (2.5 mL) was then added followed by solid sodium ascorbate (130 mg, 0.657 mmol), methyl propionate (553 mg, 0.657 mmol) and 1M aq. CuSO<sub>4</sub> solution (0.2 mL) to give a yellow solution. The reaction mixture was stirred overnight at room temperature to give a mustard-



colored suspension. Water was added until a suspension formed, filtered, washed with water, and dried to generate the title compound **420** (1.05 g, 63% yield) as a mustard-colored solid.

[0991] LRMS: (calc.) 262.1 (found) 262.2 (MH)<sup>+</sup>

Steps 3-5 N-(2-Amino-5-(thiophen-2-yl)phenyl)-1-(benzo[d][1,3]dioxol-5-ylmethyl)-1H-1,2,3-triazole-4-carboxamide (**422**)

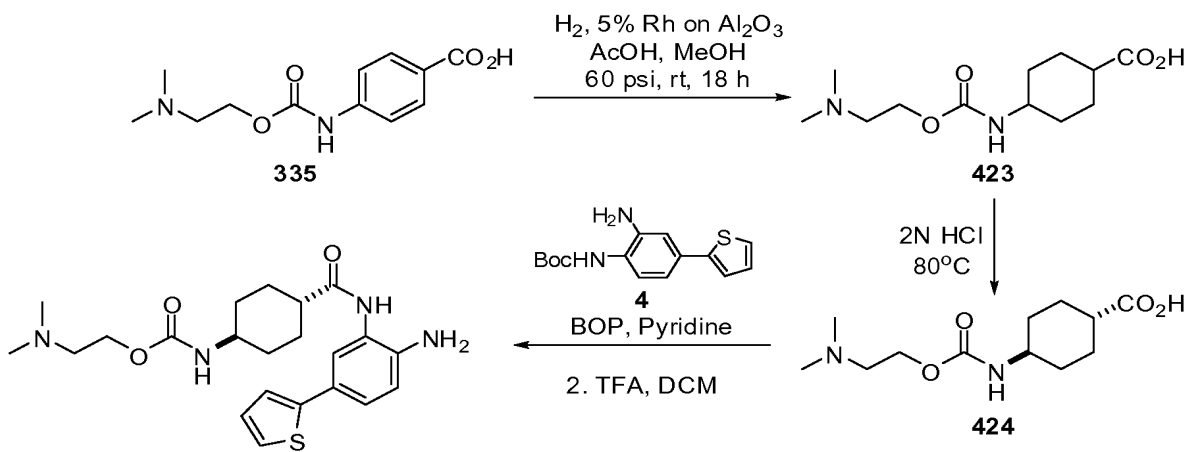
[0992] Following the general procedures **P**, **F** and **W**, the title compound **422** was obtained as a gray powder (32 mg, 16% yield, last step).

[0993] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 10.3 (s, 1H), 8.84 (s, 1H), 7.7 (s, 1H), 7.54 (m, 2H), 7.44 (m, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.11 (dd, J = 3.6, 5.2 Hz, 1H), 7.00 (s, 1H), 6.91 (s, 2H), 6.01 (s, 2H), 5.59 (s, 2H). LRMS: (calc.) 419.1 (found) 420.2 (MH)<sup>+</sup>

### Example 46a

#### 2-(Dimethylamino)ethyl (trans)-4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)cyclohexylcarbamate (**426**)

#### Scheme 46



**426: example 46a**

Steps 1-2. Trans-4-((2-(Dimethylamino)ethoxy)carbonylamino)cyclohexanecarboxylic acid (**424**)

[0994] A suspension of compound **335** (1.0 g, 3.96 mmol) and 5% Rh on Al<sub>2</sub>O<sub>3</sub> (350 mg) in AcOH (5 mL) and MeOH (5 mL) was stirred at room temperature under 60psi of hydrogen. The reaction mixture was filtered on celite and the filtrate was evaporated to afford the title compound **423** which was dissolved in 2N HCl (920 mL) and stirred at 80 °C for 18 h. The

reaction mixture was concentrated, diluted in water, cooled down to -78 °C and lyophilysed during 5 days to afford the title compound **424** as a white solid (820 mg, 82%).

[0995] LRMS: (calc.) 258.2 (found) 259.2 (MH)<sup>+</sup>.

Steps 3-4. 2-(dimethylamino)ethyl (trans)-4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)-cyclohexylcarbamate (**426**)

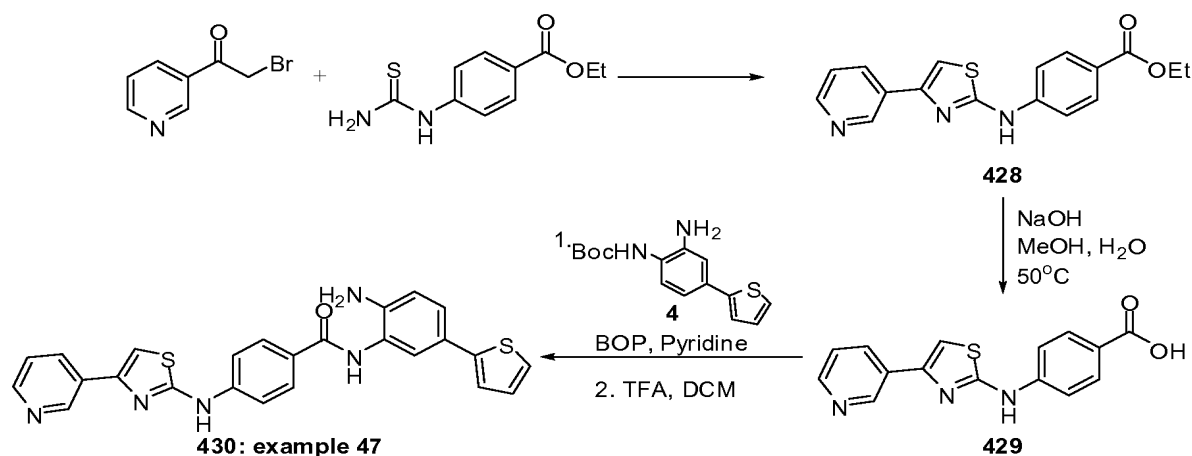
[0996] Following the general procedures **F** and **G**, the title compound **426** was obtained as an orange solid (460 mg, 81%, last step).

[0997] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.18 (s, 1H), 7.46 (d, J=4.5 Hz, 1H), 7.32 (dd, J=8.1, 2.1 Hz, 1H), 7.18 (m, 2H), 7.05 (m, 1H), 6.74 (d, J=8.2, 1H), 5.05 (s, 2H), 4.01 (t, J=5.1 Hz, 2H), 3.52 (s, 1H), 2.48 (m, 2H), 2.18 (s, 6H), 1.85 (m, 2H), 1.71 (m, 2H), 1.52 (m, 4H). LRMS: (calc.) 430.7 (found) 431.3 (MH)<sup>+</sup>.

### Example 47a

**N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(4-(pyridin-3-yl)thiazol-2-ylamino)benzamide (**430**)**

#### Scheme 47



Step 1. Ethyl 4-(4-(pyridin-3-yl)thiazol-2-ylamino)benzoate (**428**)

[0998] Ethyl 4-thioureidobenzoate (209 mg, 0.935 mmol) was added to a warm solution (50 °C) of 2-bromo-1-(pyridin-3-yl)ethanone (250 mg, 0.88 mmol) in water (5 mL) and stirred at 50 °C for 5 h. The precipitated was filtered out to afford the title compound **428** as a yellow solid (476 mg, wet) which was used without further purification.

[0999] LRMS: (calc.) 325.0 (found) 326.0 (MH)<sup>+</sup>.

Steps 2-4. N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(4-(pyridin-3-yl)thiazol-2-ylamino)-benzamide (430)

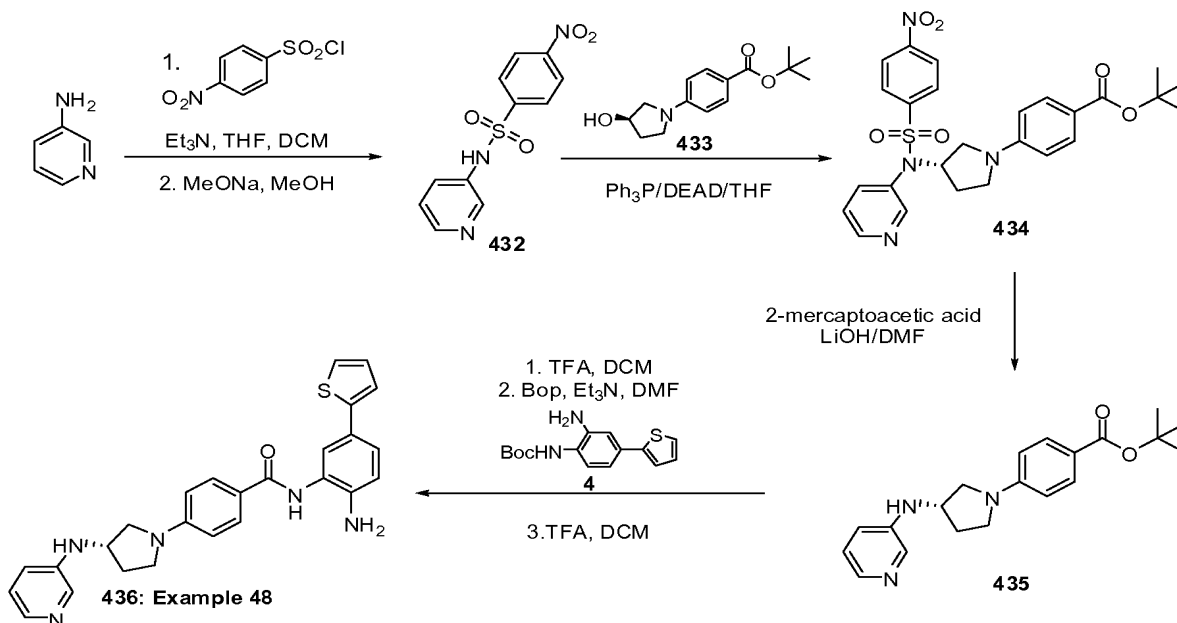
[1000] Starting from 428, the general procedures **P**, **F** and **G** were followed to afford the title compound **430** as a yellow solid (30 mg, 24%, last step, isolated as a TFA salt).

[1001]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 10.77 (s, 1H), 9.77 (s, 1H), 9.23 (s, 1H), 8.63 (d,  $J=4.5$  Hz, 1H), 8.53 (d,  $J=7.4$  Hz, 1H), 8.03 (d,  $J=8.8$  Hz, 2H), 7.85 (d,  $J=8.8$  Hz, 2H), 7.74 (s, 1H), 7.71-7.66 (m, 1H), 7.52 (d,  $J=2.2$  Hz, 1H), 7.39 (dd,  $J=5.1, 1.0$  Hz, 1H), 7.35 (dd,  $J=8.4, 2.0$  Hz, 1H), 7.29 (dd,  $J=5.1, 1.0$  Hz, 1H), 7.06 (dd,  $J=5.1, 3.5$  Hz, 1H), 6.91 (d,  $J=8.2$  Hz, 1H). LRMS: 469.58 (calc) 470.0 (found).

**Example 48a**

**(S)-N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(3-(pyridin-3-ylamino)pyrrolidin-1-yl)benzamide (436)**

**Scheme 48**



Step 1: N-p-Nosyl-3-pyridine (432):

[1002] To a stirred solution of 2-aminopyridine (3.03 g, 32.2 mmol) in THF (15 mL) were successively added DCM (30 mL), 4-nitrobenzenesulfonyl chloride (1.50g, 68.7 mmol), and  $\text{Et}_3\text{N}$  (9.88 mL, 70.9 mmol). The solution turned orange and a precipitate formed. The suspension was allowed to stir at room temperature for 1 h, solvents were evaporated under reduced pressure and the solid residue was suspended in MeOH (200 mL). To the suspension a

large excess (>10 eq) of sodium methoxide was added, the mixture was stirred at 50 °C for 3 h, quenched with HCl 1N (2 mL) and concentrated under reduced pressure at 80 °C until the volume became ~ 50 mL. The concentrated solution was further acidified with 1N HCl until neutral pH. The precipitate formed was filtered to afford the title compound (7.67 g, 85% yield).

[1003]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 10.88 (s, 1H), 8.36 (d,  $J=9.0$  Hz, 2H), 8.28 (dd,  $J=6.1$ , 1.4 Hz, 1H), 8.27 (d,  $J=2.5$  Hz, 1H), 7.50 (ddd,  $J=8.4$ , 2.7, 1.6 Hz, 1H), 7.30 (ddd,  $J=8.2$ , 4.7, 0.8 Hz, 1H). LRMS: calc. 279.0, found. 280.1 ( $\text{MH}^+$ ).

Step 2: tert-Butyl 4-((S)-3-N-p-nosyl (pyridin-3-ylamino)pyrrolidin-1-yl)benzoate (434)

[1004] To a solution of compound **432** (6.00 g, 21.5 mmol) in THF (100 mL), were successively added carbinol **433** (5.66 g, 21.5 mmol) (Compound **433** was obtained using procedure **J** starting from tert-butyl 4-fluorobenzoate compound with (R)-pyrrolidin-3-ol), triphenylphosphine (6.76 g, 25.8 mmol) and diethyl azodicarboxylate (4.06 mL, 25.8 mmol). The mixture was stirred at room temperature for 18 h and the solvent was removed *in vacuo*. The residue was purified by flash chromatography using EtOAc/Hex (40:60) as an eluent to afford the title compound **434** (4.68 g, 42% yield).

[1005]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 8.58 (dd,  $J=4.7$ , 1.4 Hz, 1H), 8.48 (d,  $J=8.0$  Hz, 2H), 8.38 (d,  $J=2.0$  Hz, 1H), 8.13 (d,  $J=9.0$ , 2H), 7.72 (d,  $J=9.0$  Hz, 2H), 7.61 (ddd,  $J=8.0$ , 2.5, 1.6 Hz, 1H), 7.39 (dd,  $J=8.2$ , 4.9 Hz, 1H), 6.43 (d,  $J=9.0$  Hz, 2H), 5.17 (quint,  $J=8.2$  Hz, 1H), 3.77 (dd,  $J=10.4$ , 7.2 Hz, 1H), 3.36 (dd,  $J=10.4$ , 6.7 Hz, 1H), 3.26 (dd,  $J=15.1$ , 7.8 Hz, 1H), 3.06 (td,  $J=12.3$ , 3.3 Hz, 1H), 2.43-2.38 (m, 1H), 2.02-1.94 (m, 1H), 1.55 (s, 9H). LRMS: calc. 524.2, found 525.3 ( $\text{MH}^+$ ).

Step 3: tert-Butyl 4-((S)-3-(pyridin-3-ylamino)pyrrolidin-1-yl)benzoate (435)

[1006] To a solution of the nitro compound **434** (4.68 g, 8.92 mmol) in DMF (45 mL), were successively added lithium hydroxide (1.31 g, 31.2 mmol) and thioglycolic acid (930  $\mu\text{L}$ , 13.4 mmol). The mixture was stirred for 3 days at room temperature, the solvent was removed *in vacuo* at 80 °C and the residue was partitioned between EtOAc and  $\text{H}_2\text{O}$ . Organic layer was collected and extracted with HCl 1N. Acidic layer was collected and neutralized with a saturated  $\text{NaHCO}_3$  solution. A white precipitate was formed which was extracted with EtOAc. The EtOAc solution was washed with brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo* to afford the title compound **435** (1.65 g, 54%yield) as a white solid.

[1007]  $^1\text{H}$  NMR: (Acetone- $d_6$ )  $\delta$  (ppm): 8.08 (d,  $J=2.2$  Hz, 1H), 7.86 (d,  $J=4.3$  Hz, 1H), 7.79 (d,  $J=9.0$  Hz, 2H), 7.09 (dd,  $J=8.2, 4.3$  Hz, 1H), 7.05 (ddd,  $J=8.2, 2.7, 1.6$  Hz, 1H), 6.57 (d,  $J=8.8$  Hz, 2H), 5.54 (d,  $J=6.5$  Hz, 1H), 4.32 (sext,  $J=5.3$  Hz, 1H), 3.78 (dd,  $J=10.2, 5.9$  Hz, 1H), 3.56 (dd,  $J=17.0, 7.2$  Hz, 1H), 3.47 (td,  $J=8.0, 5.1$  Hz, 1H), 3.31 (dd,  $J=10.2, 3.9$  Hz, 1H), 2.44 (sext.,  $J=7.8$  Hz, 1H), 2.13 (sext,  $J=5.1$  Hz, 1H), 1.56 (s, 9H). LRMS: calc. 339.2, found 340.3 ( $\text{MH}^+$ ).

Steps 4-6. (S)-N-(2-Amino-5-(thiophen-2-yl)phenyl)-4-(3-(pyridin-3-ylamino)pyrrolidin-1-yl)benzamide (436)

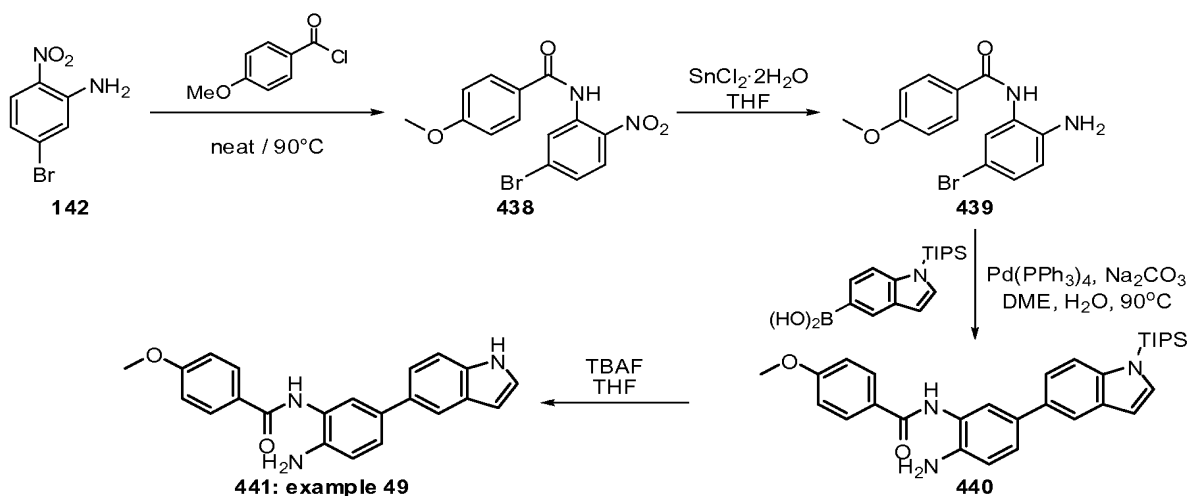
[1008] Starting from compound **435**, the general procedures **I**, **N** and **G** were followed to afford the title compound **436** as a beige solid (720 mg, 73% yield, last step).

[1009]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 9.43 (s, 1H), 8.02 (d,  $J=2.7$  Hz, 1H), 7.88 (d,  $J=8.6$  Hz, 2H), 7.79 (d,  $J=4.3$  Hz, 1H), 7.45 (d,  $J=2.0$  Hz, 1H), 7.35 (d,  $J=5.1$  Hz, 1H), 7.26 (dd,  $J=8.4, 2.0$  Hz, 1H), 7.24 (d,  $J=3.3$  Hz, 1H), 7.10 (dd,  $J=8.2, 4.1$  Hz, 1H), 7.04 (dd,  $J=5.1, 3.3$  Hz, 1H), 7.01-6.98 (m, 1H), 6.80 (d,  $J=8.4$  Hz, 1H), 6.61 (d,  $J=8.4$  Hz, 2H), 6.18 (d,  $J=6.8$  Hz, 1H), 5.07 (s, 2H), 4.20 (sext,  $J=6.8$  Hz, 1H), 3.71 (dd,  $J=9.6, 6.1$  Hz, 1H), 3.52-3.48 (m, 1H), 3.44-3.38 (m, 1H), 3.19 (dd,  $J=9.8, 3.5$  Hz, 1H), 2.32 (sext,  $J=6.3$  Hz, 1H), 1.98 (sext,  $J=5.9$  Hz, 1H). LRMS: 455.6 (calc) 456.1(found).

### Example 49a

#### N-(2-Amino-5-(1H-indol-5-yl)phenyl)-4-methoxybenzamide (441)

#### Scheme 49



Steps 1-2. N-(2-Amino-5-bromo-phenyl)-4-methoxy-benzamide (439)

[1010] In a flame dried, round bottom flask, the aniline **142** (10.66 g, 49.09 mmol) and 4-methoxybenzoyl chloride (8.37 g, 49.09 mmol) were added. The mixture was heated to 90 °C. The melted solids were stirred overnight to give compound **438** as a yellow-brown solid. THF (250 mL) was then added and the solution was treated with  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (55.38 g, 245.45 mmol) and stirred at room temperature for 2 h. Approx. half of the THF was evaporated then EtOAc and sat.  $\text{NaHCO}_3$  were added. The precipitated tin salt was taken out by filtration and a work-up was done on the filtrate with EtOAc. The combined organic layers were washed with water and brine and dried over  $\text{MgSO}_4$ . Most of the EtOAc was evaporated then hexane was added and the precipitate was collected by filtration to give the title compound **439** as a beige powder (13.40 g, 85% yield).

[1011]  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  (ppm): 9.52 (s, 1H), 7.93 (d,  $J=9.0$  Hz, 2H), 7.34 (d,  $J=2.3$  Hz, 1H), 7.08 (dd,  $J=8.6, 2.3$  Hz, 1H), 7.02 (d,  $J=9.0$  Hz, 2H), 6.71 (d,  $J=8.6$  Hz, 1H), 5.10 (s, 2H), 3.82 (s, 3H).

Step 3. N-(2-Amino-5-(1-(triisopropylsilyl)-1H-indol-5-yl)phenyl)-4-methoxybenzamide (440)

[1012] Starting from compound **439**, the general procedure **B** was followed (using no POT and  $\text{Na}_2\text{CO}_3$  instead  $\text{K}_2\text{CO}_3$ ), to afford the title compound **440** (14 mg, 5% yield).

[1013] LRMS: 513.3 (calc) 514.5(found).

Step 4. N-(2-Amino-5-(1H-indol-5-yl)phenyl)-4-methoxybenzamide (441)

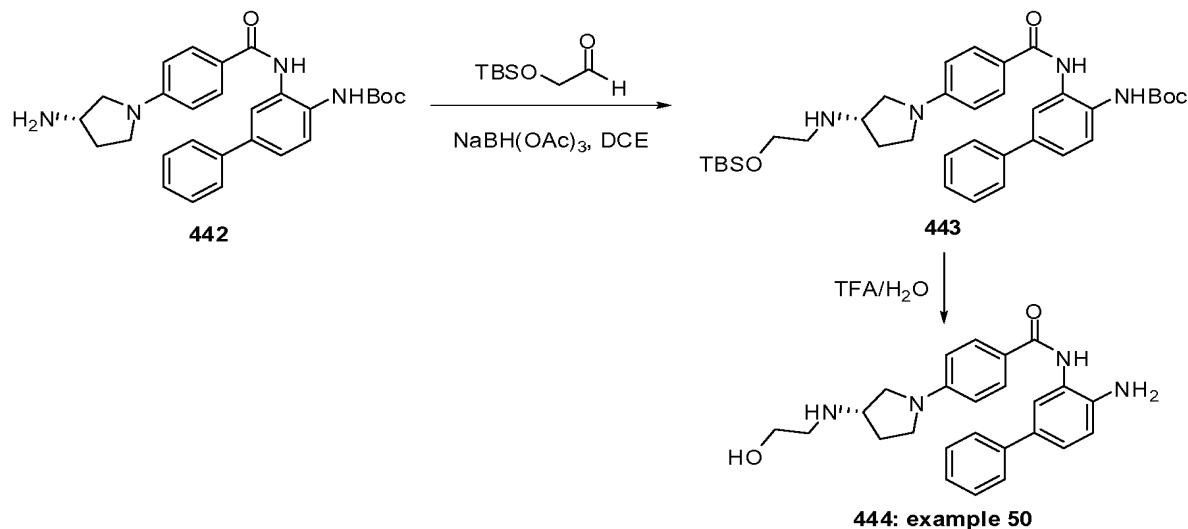
[1014] TBAF (26  $\mu\text{L}$ ) was added to a solution of **440** (14 mg, 0.027 mmol) in THF (50  $\mu\text{L}$ ), stirred 1 h at room temperature, diluted with ethyl, washed with water, the organic layer was dried ( $\text{MgSO}_4$ ), filtered and concentrated. The compound was purified by preparative TLC to afford the title compound **441** (5.4 mg, 56% yield).

[1015] LRMS: 357.4 (calc) 358.3 (found).

**Example50**

**(S)-N-(4-Aminobiphenyl-3-yl)-4-(3-(2-hydroxyethylamino)pyrrolidin-1-yl)benzamide (444)**

Scheme 50



Step 1. (S)-tert-Butyl 3-(4-(3-(2-(tert-butyldimethylsilyloxy)ethylamino)pyrrolidin-1-yl)benzamido)biphenyl-4-ylcarbamate (**443**)

[1016] Starting from (S)-pyrrolidin-3-amine and tert-butyl 4-fluorobenzoate, the compound **442** was synthesized the same way as compound **404** (Scheme 42, example 42a) by following the general procedures **J**, **T**, **I**, **F** (using compound **322**) and **R**. Then, starting with **442**, the general procedure **DD** was followed to afford the title compound **443** as beige foam (133 mg, 22% yield).

[1017] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ (ppm): 9.66 (s, 1H), 8.76 (bs, 1H), 7.84 (m, 3H), 7.65 (dd, 7.60 (d, J=8.4 Hz, 1H), 7.48 (m, 1H), 7.45 (d, J=7.6 Hz, 2H), 7.35 (tt, J=7.2 Hz, 1H), 6.59 (d, J=8.8 Hz, 2H), 3.64 (t, J=6.0 Hz, 2H), 3.50 (dd, J=9.8, 6.2 Hz, 1H), 3.42 (m, 2H), 3.31 (m, 1H), 3.07 (dd, J=10.0, 4.8 Hz, 1H), 2.68 (td, J=6.0, 2.8 Hz, 2H), 2.13 (sext, J=6.2 Hz, 1H), 1.81 (sext, J=6.2 Hz, 1H), 1.47 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H). LRMS: (Calc): 630.4 (found) 631.4 (MH)<sup>+</sup>.

Step 2. (S)-N-(4-Aminobiphenyl-3-yl)-4-(3-(2-hydroxyethylamino)pyrrolidin-1-yl)benzamide (**444**)

[1018] A solution of **443** (0.13 g, 0.206 mmol) in TFA (0.392 mL) and water (0.021 mL) was stirred for 2 h at room temperature. The solvent was evaporated and the residue obtained was dissolved in EtOAc, washed with sat NaHCO<sub>3</sub> and sat NaCl. The organic layer was dried with MgSO<sub>4</sub>, filtered and concentrated to a brown solid. Trituration in Et<sub>2</sub>O generated the title compound **444** as a beige powder (70 mg, 82% yield).

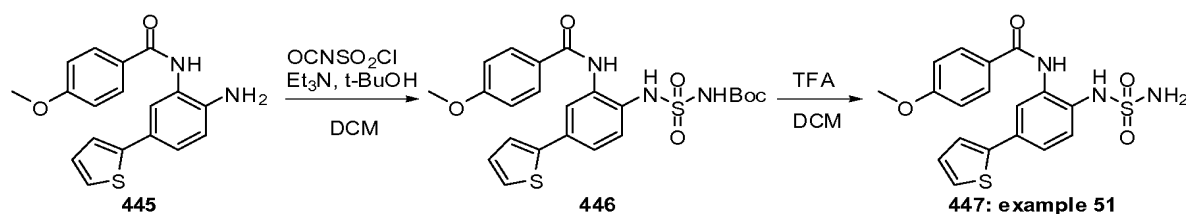
[1019]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 9.48 (s, 1H), 7.90 (d,  $J=8.8$  Hz, 2H), 7.56 (dd,  $J=8.4$ , 1.2 Hz, 2H), 7.51 (d,  $J=2.4$  Hz, 1H), 7.39 (t,  $J=7.8$  Hz, 2H), 7.30 (dd,  $J=8.2$ , 2.2 Hz, 1H), 7.24 (tt,  $J=7.4$ , 1.3 Hz, 1H), 6.86 (d,  $J=8.4$  Hz, 1H), 6.59 (d,  $J=8.8$  Hz, 2H), 5.04 (bs, 2H), 4.80 (bs, 1H), 3.55 (bs, 3H), 3.45 (m, 1H), 3.30 (m, 1H), 3.21 (m, 1H), 2.79 (bs, 2H), 2.21 (m, 1H), 1.98 (bs, 1H).

[1020] LRMS Calc 416.2; Found: 417.3 (MH) $^+$ .

### Example 51

#### 4-Methoxy-N-(2-(sulfamoylamino)-5-(thiophen-2-yl)phenyl)benzamide (447)

#### Scheme 51



#### Step 1. tert-Butyl N-(2-(4-methoxybenzamido)-4-(thiophen-2-yl)phenyl)sulfamoyl-carbamate (446)

[1021] Starting from compound **4** and 4-methoxybenzoyl chloride the compound **445** was synthesized following the general procedure **K** and **G**. Then, t-BuOH (0.08 mL, 0.80 mmol) was added dropwise to a solution at 0 °C of sulfurisocyanatidic chloride (0.07 mL, 0.80 mmol) in DCM (20 mL) and stirred for 20 min. A solution of compound **445** (260 mg, 0.80 mmol) in DCM (2 mL) and Et<sub>3</sub>N (0.3 mL, 2.40 mmol) was added, stirred at room temperature for 18 h, quenched with water, extracted 3 times with DCM, dried over MgSO<sub>4</sub> and concentrated. The residue was purified by flash chromatography using 5% MeOH in DCM as an eluent to afford the title compound **446** (365 mg, 90%) as a white solid.

[1022] LRMS Calc 503.1; Found: 526.2 (M+Na) $^+$ .

#### Step 2. 4-Methoxy-N-(2-(sulfamoylamino)-5-(thiophen-2-yl)phenyl)benzamide (447)

[1023] Following the general procedure **G**, the title compound **447** was obtained as a white solid (70 mg, 21 % yield).

[1024]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 9.70 (s, 1H), 8.81 (s, 1H), 8.20 (s, 1H), 7.94 (d,  $J=8.9$ Hz, 2H), 7.50 (m, 4H), 7.22 (s, 2H), 7.14 (m, 3H), 3.84 (s, 3H).

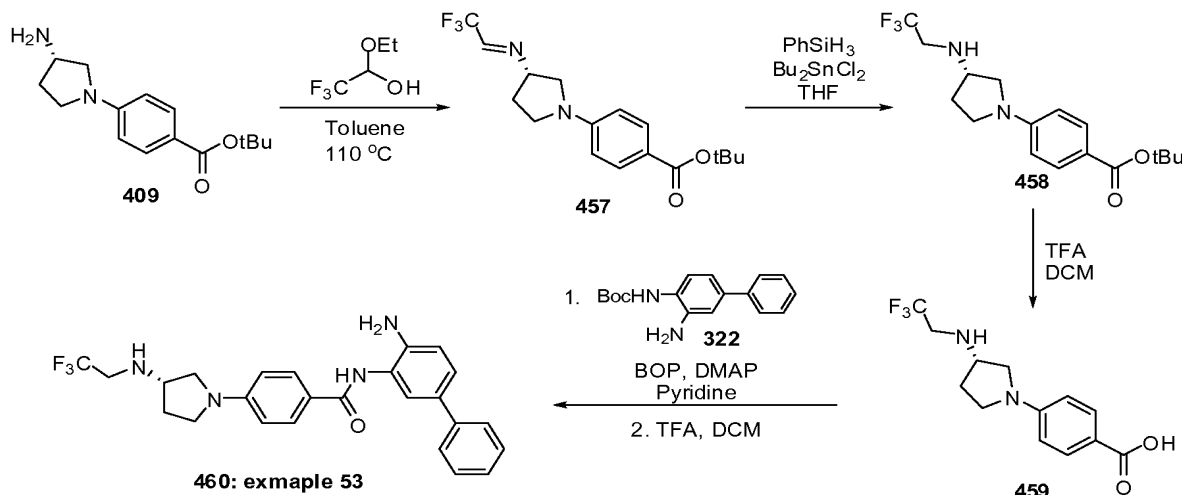
[1025] LRMS: (calc.) 403.5 (found) 404.0 (MH) $^+$



## Example 53

(S)-N-(4-Aminobiphenyl-3-yl)-4-(3-(2,2,2-trifluoroethylamino)pyrrolidin-1-yl)benzamide  
(460)

## Scheme 53

Step 1. 4-(3-(2,2,2-Trifluoroethylideneamino)pyrrolidin-1-yl)benzoate (457)

[1026] A solution of compound **409** (1.2 g, 4.57 mmol) and 1-ethoxy-2,2,2-trifluoroethanol (1.65 g, 11.4 mmol) in toluene (23 mL) was heated to 120 °C for 16 h with a Dean-Stark apparatus. More 2,2,2-trifluoroethanol (1.65 g, 11.4 mmol) was added and the reaction was stirred for an extra 2 h. The solvent was then evaporated to afford the title compound **457** (1.26 g, 81% yield)

[1027]  $^1\text{H}$  NMR (MeOD- $d_4$ )  $\delta$  (ppm): 8.98 (d,  $J=5.7$  Hz, 2H), 8.57 (t,  $J=7.8$  Hz, 1H), 8.09 (t,  $J=7.2$  Hz, 2H), 7.84 (d,  $J=1.6$  Hz, 1H), 7.59 (dd,  $J=7.0, 1.4$  Hz, 2H), 7.51 (dt,  $J=7.2, 2.0$  Hz, 1H), 7.47-7.40 (m, 2H), 7.40-7.31 (m, 2H), 4.62 (t,  $J=7.6$  Hz, 2H), 2.40 (t,  $J=7.2$  Hz, 2H), 2.02 (quin,  $J=7.0$  Hz, 2H), 1.70 (quin,  $J=7.0$  Hz, 2H), 1.50-1.45 (m, 6H)

Step 2. (S)-tert-Butyl 4-(3-(2,2,2-trifluoroethylamino)pyrrolidin-1-yl)benzoate (458)

[1028] Dibutyltin dichloride (28 mg, 0.09 mmol) and phenylsilane (365 mg, 3.37 mmol) were added to a suspension of **457** (1.05 g, 3.07 mmol), in THF (6.1 mL). The reaction mixture was stirred for 48 h at room temperature, diluted with AcOEt, washed with water and brine, dried over  $\text{MgSO}_4$ , filtered and concentrated. The residue was purified by flash chromatography to afford the title compound **458** (647 mg, 61% yield) as a white solid.

[1029] LRMS: (calc.) 344.2 (found) 345.2 (MH) $^+$ .

Steps 3-5. (S)-N-(4-Aminobiphenyl-3-yl)-4-(3-(2,2,2-trifluoroethylamino)pyrrolidin-1-yl)benzamide (460)

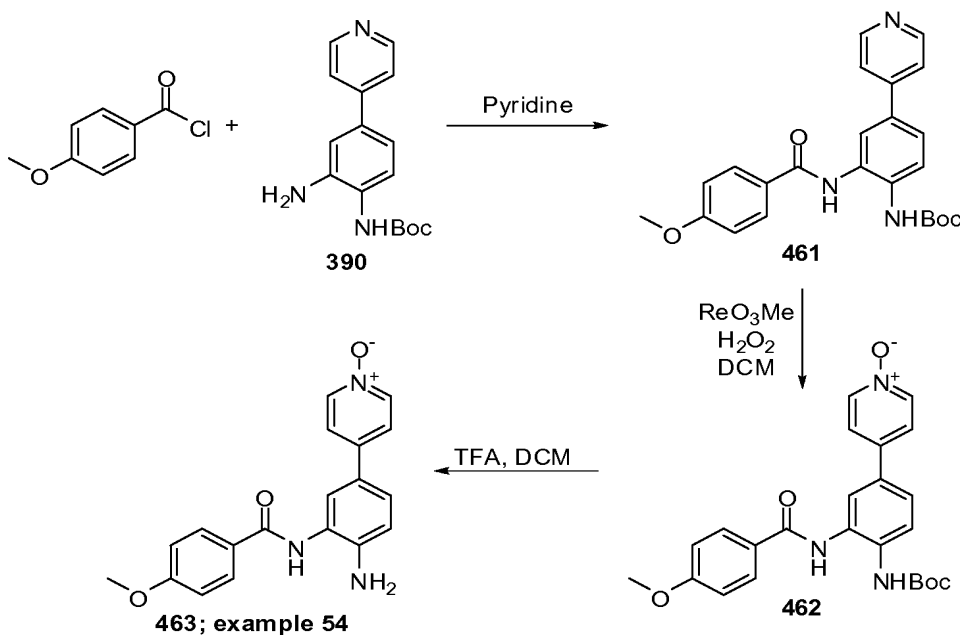
[1030] Starting from compound **458** the general procedures **I**, **F** and **G** were followed to afford the title compound **460** (61 mg, 15% yield, last step).

[1031]  $^1\text{H}$  NMR (MeOD- $d_4$ )  $\delta$  (ppm): 7.90 (d,  $J=8.8$  Hz, 2H), 7.56 (dd,  $J=8.2$ , 1.4 Hz, 2H), 7.46 (d,  $J=2.2$  Hz, 1H), 7.36 (t,  $J=8.2$  Hz, 2H), 7.35 (dd,  $J=8.2$ , 2.2 Hz, 1H), 7.23 (tt,  $J=7.2$ , 1.4 Hz, 1H), 6.97 (d,  $J=8.2$  Hz, 1H), 6.63 (d,  $J=9.0$  Hz, 2H), 3.64-3.33 (m, 6H), 3.22-3.14 (m, 1H), 3.22-3.14 (m, 1H), 2.32-2.22 (m, 1H), 2.00-1.80 (m, 1H). LRMS: (calc.) 454.49 (found) 455.3 (MH) $^+$

**Example 54**

**4-(4-Amino-3-(4-methoxybenzamido)phenyl)pyridine 1-oxide (463)**

**Scheme 54**



Step 1. tert-Butyl 2-(4-methoxybenzamido)-4-(pyridin-4-yl)phenylcarbamate (461)

[1032] Starting from compound **390** and 4-methoxybenzoyl chloride the general procedure **K** was followed to afford the title compound **461** as orange foam (560 mg, 76% yield).

[1033]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 9.85 (br s, 1H), 8.83 (br s, 1H), 8.62 – 8.59 (m, 2H), 7.98 – 7.94 (m, 3H), 7.75 – 7.64 (m, 4H), 7.08 (d,  $J=9.0$  Hz, 2H), 3.84 (s, 3H), 3.33 (s, 3H), 1.45 (s, 9H).

Step 2. 4-(4-(tert-butoxycarbonylamino)-3-(4-methoxybenzamido)phenyl)pyridine 1-oxide (462)

[1034] A solution of compound **461** (0.55 g, 1.31 mmol) and  $\text{ReO}_3\text{Me}$  (33 mg, 0.13 mmol) in DCM (10 mL) was stirred 5 min, 35%  $\text{H}_2\text{O}_2$  (0.14 mL, 1.53 mmol) was added and the reaction was stirred at room temperature for 2 h. The reaction mixture was quenched with water, and AcOEt was added. The white precipitate was filtered and washed with AcOEt and MeOH (5 mL) to afford the title compound **462** (350 mg, 61%) as a white solid.

[1035]  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  (ppm): 9.83 (s, 1H), 8.81 (s, 1H), 8.23 (d,  $J=7.2$  Hz, 2H), 7.96 (d,  $J=8.8$  Hz, 2H), 7.91 (d,  $J=2.0$  Hz, 1H), 7.74 – 7.70 (m, 3H), 7.64 – 7.61 (m, 1H), 7.08 (d,  $J=9.0$  Hz, 2H), 3.84 (s, 3H), 1.45 (s, 9H).

Step 3. 4-(4-Amino-3-(4-methoxybenzamido)phenyl)pyridine 1-oxide (463)

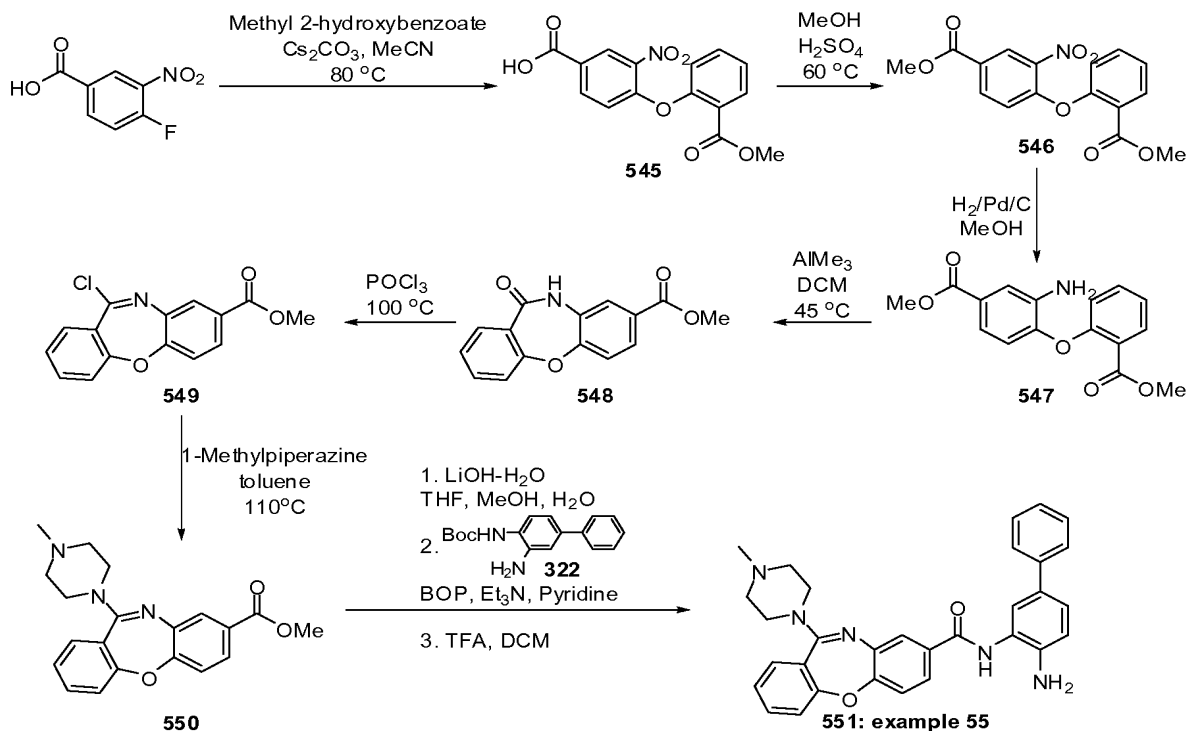
[1036] Starting from compound **462** the general procedure **G** was followed to afford the title compound **463** as a dark yellow solid (110 mg, 42% yield).

[1037]  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  (ppm): 9.61 (s, 1H), 8.13 (d,  $J=7.2$  Hz, 2H), 7.98 (d,  $J=8.8$  Hz, 2H), 7.62-7.59 (m, 3H), 7.44 (dd,  $J=8.6, 2.3$  Hz, 1H), 7.04 (d,  $J=9.0$  Hz, 2H), 6.85 (d,  $J=8.4$  Hz, 1H), 5.34 (s, 2H), 3.83 (s, 3H). LRMS: (calc.) 335.1 (found) 336.3 (MH)+

**Example 55**

**(E)-N-(4-Aminobiphenyl-3-yl)-11-(4-methylpiperazin-1-yl)dibenzo[b,f][1,4]oxazepine-8-carboxamide (551)**

## Scheme 55

Step 1. 4-(2-(Methoxycarbonyl)phenoxy)-3-nitrobenzoic acid (**545**)

[1038] 4-Fluoro-3-nitrobenzoic acid (5.0 g, 27.0 mmol), methyl 2-hydroxybenzoate (4.11 g, 27.0 mmol) and  $\text{Cs}_2\text{CO}_3$  (18.49 g, 56.7 mmol) were dissolved in acetonitrile (100 mL) and stirred at 80 °C for 3 h. The reaction mixture was diluted with AcOEt and washed with 1M HCl and water. The organic layer was separated, dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated via rotary evaporation to afford the title compound **545** (7.55 g, 88%) as a light yellow foam.

[1039]  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  (ppm): 8.49 (d,  $J$  = 2.1 Hz, 1H), 8.08 (dd,  $J$  = 8.8, 2.2 Hz, 1H), 8.00 – 7.97 (m, 1H), 7.79 – 7.74 (m, 1H), 7.49 (td,  $J$  = 7.6, 1.2 Hz, 1H), 7.41 (dd,  $J$  = 8.2, 0.8 Hz, 1H), 6.85 (d,  $J$  = 8.8 Hz, 1H), 3.63 (s, 3H).

Step 2. Methyl 4-(2-(methoxycarbonyl)phenoxy)-3-nitrobenzoate (**546**)

[1040] Concentrated  $\text{H}_2\text{SO}_4$  (3 mL) was added to a solution of compound **545** (7.5 g, 23.64 mmol) in MeOH (80 mL) and stirred at 60 °C for 16 h. MeOH was removed under vacuum and the crude product was dissolved in AcOEt and washed with water. The organic layer was separated, dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated via rotary evaporation to afford the title compound **546** (6.2 g, 79%) as a light yellow solid.

[1041]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 8.52 (d,  $J$  = 2.1 Hz, 1H), 8.09 (dd,  $J$  = 9.0, 2.4 Hz, 1H), 8.00 (dd,  $J$  = 8.8, 1.3 Hz, 1H), 7.80 – 7.75 (m, 1H), 7.50 (td,  $J$  = 7.4, 1.0 Hz, 1H), 7.42 (dd,  $J$  = 8.0, 1.0 Hz, 1H), 6.87 (d,  $J$  = 8.8 Hz, 1H), 3.86 (s, 3H), 3.62 (s, 3H).

Step 3. Methyl 3-amino-4-(2-(methoxycarbonyl)phenoxy)benzoate (547)

[1042] Starting from compound **546** the general procedure C was followed to afford the title compound **547** (535 mg, 95% yield) as a yellow oil.

[1043]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 7.82 (dd,  $J$  = 7.8, 1.6 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.43 (d,  $J$  = 2.1 Hz, 1H), 7.25 (td,  $J$  = 7.6, 1.2 Hz, 1H), 7.11 (dd,  $J$  = 8.4, 2.1 Hz, 1H), 6.98 (dd,  $J$  = 8.4, 1.0 Hz, 1H), 6.64 (d,  $J$  = 8.4 Hz, 1H), 5.31 (br s, 2H), 3.78 (s, 3H), 3.72 (s, 3H).

Step 4. Methyl 11-oxo-10,11-dihydrodibenzo[b,f][1,4]oxazepine-8-carboxylate (548)

[1044] A solution of compound **547** (3.2 g, 10.62 mmol) and  $\text{AlMe}_3$  (6.37 mL, 12.75 mmol) in DCM (40 mL) was stirred at 45 °C for 16 h and quenched with water. The reaction was diluted with AcOEt, washed with water and 1M HCl. The organic layer was separated, dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated via rotary evaporation. The residue was triturated with AcOEt, filtered, washed with AcOEt and was purified via Isco employing a 0 to 50% AcOEt in hexanes solvent gradient to afford the title compound **548** (1.01 g, 35%) as a white solid.

[1045]  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  (ppm): 10.68 (s, 1H), 7.79 – 7.75 (m, 2H), 7.70 (dd,  $J$  = 8.4, 2.1 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.45 (d,  $J$  = 8.4 Hz, 1H), 7.38 – 7.30 (m, 2H), 3.82 (s, 3H).

Step 5. (E)-Methyl 11-chlorodibenzo[b,f][1,4]oxazepine-8-carboxylate (549)

[1046] Compound **548** (1.00 g, 3.71 mmol) was suspended in  $\text{POCl}_3$  (20 mL). The reaction mixture was stirred at 100 °C for 3h.  $\text{POCl}_3$  was removed on rotovap. The crude product was dissolved in ethyl acetate and washed with 2M  $\text{Na}_2\text{CO}_3$  solution then with  $\text{NaHCO}_3$  saturated solution and finally with brine. The organic layer was separated and dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated via rotary evaporation to afford compound **549** (1.069 g, 100%) as a orange solid that was taken on without further purification.

Step 6. (E)-Methyl 11-(4-methylpiperazin-1-yl)dibenzo[b,f][1,4]oxazepine-8-carboxylate (550)

[1047] Compound **549** (1.06 g, 3.68 mmol) and 1-methylpiperazine (0.818 mL, 7.37 mmol) were dissolved in toluene (40 mL) and stirred at 110 °C for 16h. The toluene was removed on the rotary evaporator. The crude product was dissolved in ethyl acetate and washed with water. The organic layer was separated and dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated via rotary

evaporation. The residue was purified via Isco employing a 0 to 50% methanol: ethyl acetate solvent gradient to afford compound **550** (0.86 g, 66%) as a white solid.

[1048]  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  (ppm): 7.59 – 7.53 (m, 3H), 7.42 – 7.36 (m, 2H), 7.31 (td,  $J = 7.4, 1.2$  Hz, 1H), 7.27 (d,  $J = 8.2$  Hz, 1H), 3.78 (s, 3H), 3.49 (br s, 4H), 2.47 – 2.43 (m, 4H), 2.21 (s, 3H).

Steps 7-9. (E)-N-(4-Aminobiphenyl-3-yl)-11-(4-methylpiperazin-1-yl)dibenzo[b,f][1,4]-oxazepine-8-carboxamide (**551**)

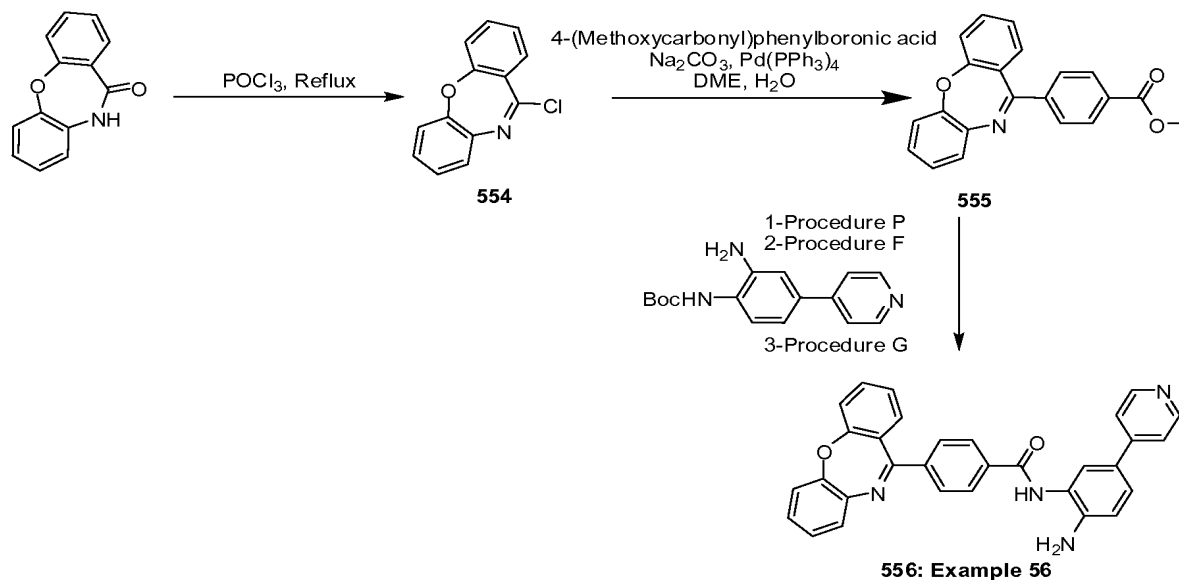
[1049] Starting from compound **550** the general procedures **P**, **F** and **G** were followed to afford the title compound **551** as a white solid (120 mg, 90% yield, last step).

[1050]  $^1\text{H}$  NMR ( $\text{MeOD-d}_4$ )  $\delta$  (ppm): 7.76 (d,  $J=2.2$  Hz, 1H), 7.66 (dd,  $J=8.2, 2.2$  Hz, 1H), 7.57 - 7.53 (m, 3H), 7.46 - 7.44 (m, 2H), 7.38 - 7.21 (m, 7H), 6.96 (d,  $J=8.4$  Hz, 1H), 3.60 (br s, 4H), 2.61 (br s, 4H), 2.38 (s, 3H). LRMS: (calc.) 503.2 (found) 504.5 ( $\text{MH}^+$ ).

### Example 56

**(Z)-N-(2-amino-5-(pyridin-4-yl)phenyl)-4-(dibenzo[b,f][1,4]oxazepin-11-yl)benzamide (**556**)**

#### Scheme 56



Step 1: (E)-11-Chlorodibenzo[b,f][1,4]oxazepine (**554**)

[1051] A solution of 10,11-dihydrodibenz[b,f][1,4]oxazepin-11-one (1.00 g, 4.74 mmol) and phosphorus oxychloride (40 mL) was stirred for 5 h at reflux. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved

into AcOEt and washed with water and brine. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give an orange oil. The residue was purified by silica gel column chromatography with EtOAc (10%) in hexanes to afford **554** (939 mg, 86%) as a yellow solid. LRMS (ESI): (calc) 229.0 (found) 230.1 (MH)<sup>+</sup>.

Step 2: (Z)-Methyl 4-(dibenzo[b,f][1,4]oxazepin-11-yl)benzoate (**555**)

[1052] To a solution of **554** (229 mg, 1.00 mmol) in DME (3 mL) was added 4-methoxycarbonylphenylboronic acid (216 mg, 1.20 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.065 mg, 0.056 mmol) and 2 N Na<sub>2</sub>CO<sub>3(aq)</sub> (1.5 mL, 3.0 mmol). The reaction mixture was stirred for 2 h at 90 °C. The solution was then cooled at room temperature and poured into AcOEt. The organic layer was washed with water, brine and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give a yellow oil. The residue was purified by silica gel column chromatography with EtOAc (15%) in hexanes to afford **555** (327 mg, 99%) as a yellow foam. LRMS (ESI): (calc) 329.1 (found) 330.3 (MH)<sup>+</sup>.

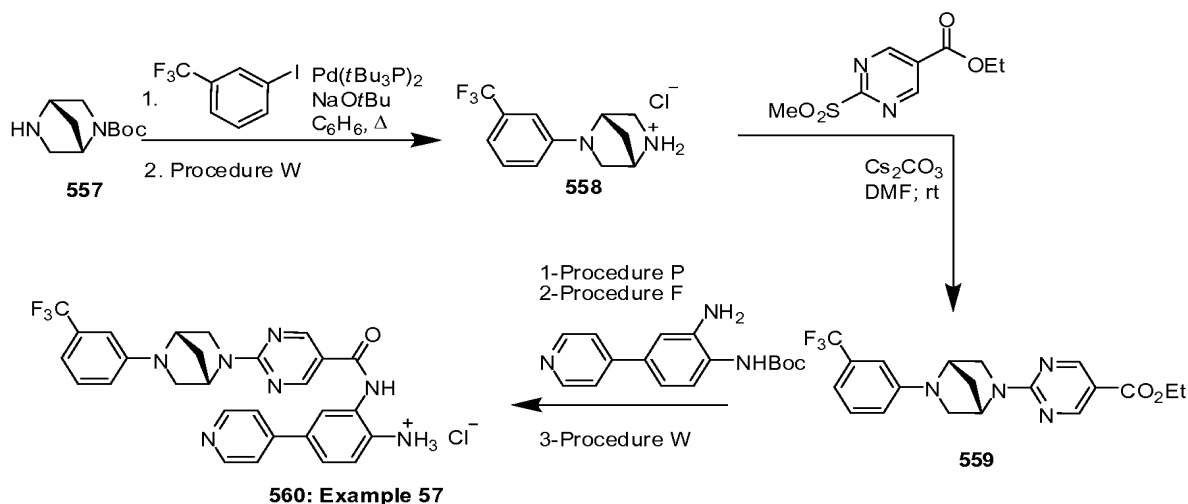
Step 3-5: (Z)-N-(2-amino-5-(pyridin-4-yl)phenyl)-4-(dibenzo[b,f][1,4]oxazepin-11-yl)benzamide (**556**)

[1053] Starting from compound **555** the general procedures **P**, **F** and **G** were followed to afford the title compound **556** as a yellow solid (100 mg, 19 % yield, last step). <sup>1</sup>H NMR (DMSO) δ (ppm) 1H: 9.91 (s, 1H), 8.50 (d, J= 5.6 Hz, 2H), 8.14 (d, J= 8.4 Hz, 2H), 7.89 (d, J= 8.4 Hz, 2H), 7.69-7.64 (m, 2H), 7.58 (d, J=6.4 Hz, 2H), 7.52 (dd, J= 2.4, 8.4 Hz, 1H), 7.46-7.43 (m, 2H), 7.34-7.27 (m, 4H), 7.19 (dd, J= 1.6, 7.6 Hz, 1H), 6.89 (d, J= 8.4 Hz, 1H), 5.42 (s, 2H). LRMS (ESI): (calc) 482.5 (found) 483.4 (MH)<sup>+</sup>.

**Example 57**

**4-(pyridin-4-yl)-2-(2-((1*S*,4*S*)-5-(3-(trifluoromethyl)phenyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidine-5-carboxamido)benzenaminium chloride (**560**)**

## Scheme 57



Step 1: (1S,4S)-5-(3-(trifluoromethyl)phenyl)-5-aza-2-azoniabicyclo[2.2.1]heptane chloride (558)

[1054] (S,S)-tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**557**) (7.3 g, 36.8 mmol) and bis(tri-*t*-butylphosphine)palladium(0) (0.05 g, 0.098 mmol) were dissolved in benzene (60 mL) under a nitrogen atmosphere to give an orange suspension. 3-Iodobenzotrifluoride (6.93 mL, 47.9 mmol), and sodium tert-butoxide (7.78 g, 81 mmol) were then added and the mixture left to stir at 110 °C overnight. The reaction was cooled to room temperature, filtered through Celite® and the filtrate was decolorized with activated charcoal. The solvent was removed in vacuo and the solid residue suspended in hexanes and triturated and filtered to get the carbamate (8.9g.) as an off-white powder. To this powder was added dioxane (25.7 ml) to give a yellow-orange suspension that was cooled to 0 °C and a solution of hydrogen chloride in dioxane (4M, 64.3 mL, 257 mmol) was added drop-wise. The solid dissolved and the mixture was left to return to room temperature over 4h. The suspension was filtered to get the hydrochloride salt **558** as a tan solid (6.82g, 66%). LRMS: 243.1 (calc) 243.1 (found).

Step 2: ethyl 2-((1S,4S)-5-(3-(trifluoromethyl)phenyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)pyrimidine-5-carboxylate (559)

[1055] Compound **558** (500 mg, 1.794 mmol) and cesium carbonate (1461 mg, 4.49 mmol) were suspended in DMF (5 mL) to give a yellow suspension. Ethyl 2-(methylsulfonyl)pyrimidine-5-carboxylate (496 mg, 2.153 mmol) was then added and the reaction was stirred at room temperature for 3 days. The mixture was diluted with water and



ethyl acetate. The organic layer was washed twice with water then brine and dried with  $\text{MgSO}_4$ . The solvent was removed *in vacuo* and the residue was purified by column chromatography (25-50% EtOAc in Hexanes) to obtain compound **559** as a white solid (313 mg, 45%). LRMS: 392.1 (found) 393.2 ( $\text{MH}^+$ ).

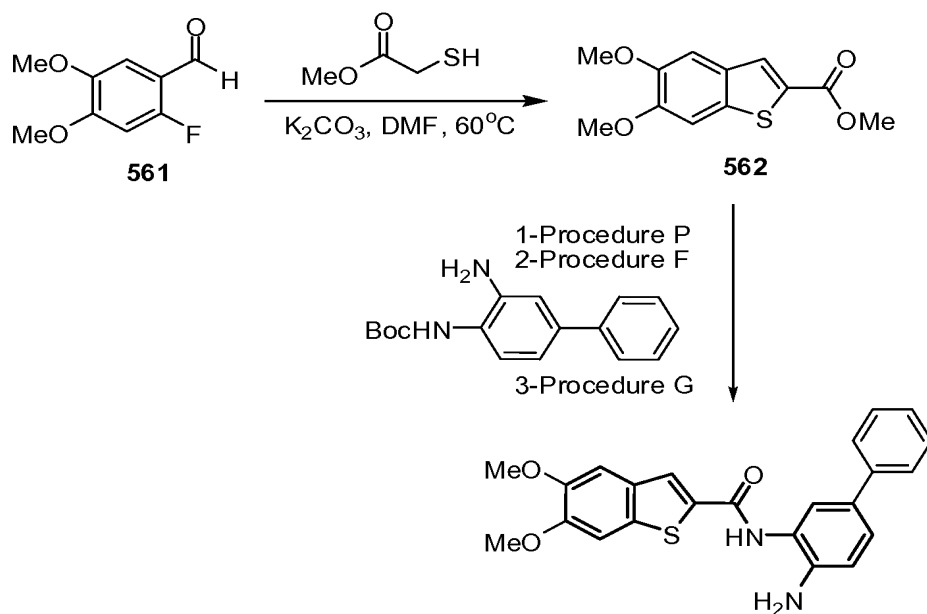
Step 3-5: 4-(pyridin-4-yl)-2-(2-(((1*S*,4*S*)-5-(3-(trifluoromethyl)phenyl)-2,5-diazabicyclo[2.2.1]-heptan-2-yl)pyrimidine-5-carboxamido)benzenaminium chloride (**560**)

[1056] Starting from compound **559** the general procedures **P**, **F** and **W** were followed to afford the title compound **560** as an orange solid (17 mg, 29 % yield, last two steps).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  (ppm): 1H: 9.10 (s, 1H), 8.95 (s, 1H), 8.69 (d,  $J = 6$  Hz, 2H), 8.28 (d,  $J = 5.6$  Hz, 2H), 7.97 (s, 1H), 7.89 (d,  $J = 8.4$  Hz, 1H), 7.35 (t,  $J = 7.6$  Hz, 1H), 7.20 (d,  $J = 8.4$  Hz, 1H), 6.91 (m, 3H), 5.33 (s, 1H), 4.82 (s, 1H), 3.80 (m, 4H), 2.28 (m, 2H). LRMS: (calc) 531.2 (found) 532.6 ( $\text{MH}^+$ ).

### Example 58

**N-(4-aminobiphenyl-3-yl)-5,6-dimethoxybenzo[b]thiophene-2-carboxamide (**563**)**

#### Scheme 58



**563: Example 58**

Step 1: Methyl 5,6-dimethoxybenzo[b]thiophene-2-carboxylate (**562**)

To a stirred solution of **561** (1.09 g, 5.92 mmol) in DMF (20 mL) was added methyl thioglycolate (6.51 mmol, 0.58 mL) and potassium carbonate (2.45 g, 17.76 mmol). The

resulting mixture was heated to 60 °C and left to stir for 15 hours. The DMF was removed via rotary evaporation and aqueous extraction was performed with ethyl acetate and water. The organic phase was separated and dried with sodium sulfate before the solvent was removed under reduced pressure and the resulting solid was dried under vacuum. This afforded **562** as a white solid (1.14 g, 77%). <sup>1</sup>H NMR (DMSO) δ (ppm): 8.00 (s, 1H), 7.58 (s, 1H), 7.47 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H).

Step 2-4: N-(4-aminobiphenyl-3-yl)-5,6-dimethoxybenzo[b]thiophene-2-carboxamide (**563**)

[1057] Starting from compound **562** the general procedures **P**, **F** and **G** were followed to afford the title compound **563** as a yellow solid (38.6 mg, 41 % yield, step).

[1058] <sup>1</sup>H NMR (DMSO) δ (ppm) 9.90 (s, 1H), 8.18 (s, 1H), 7.60 - 7.52 (m, 4H), 7.44 - 7.33 (m, 4H), 7.25 (t, J=7.4 Hz, 1H), 6.88 (d, J=8.4 Hz, 1H), 5.16 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H). LRMS: (calc) 404.5 (found) 405.4 (MH)<sup>+</sup>.

[1059] The general procedures **A** to **HH** used to synthesize compounds of this invention are described in the Table 1. A specific example of each general procedure is provided in the indicated step of a particular example. Substrates and methods may be modified and/or adapted in known ways in order to facilitate the synthesis of the compounds within the scope of the present invention.

Table 21: General procedures and reaction conditions

Proc	Sc	Ex	Step	Reaction Conditions
<b>A</b>	1	1a	1	$\text{R}^1\text{-NH}_2 \xrightarrow[2. \text{NaOH, THF, } 80^\circ\text{C}]{1. \text{Boc}_2\text{O, DMAP, THF}} \text{R}^1\text{-}\overset{\text{H}}{\underset{\text{Boc}}{\text{N}}}$
<b>B</b>	1	1a	2	$\text{Ar}^1\text{-Br} + \text{Ar}^2\text{-B(OH)}_2 \xrightarrow[\text{DME, H}_2\text{O; } 80^\circ\text{C}]{\text{Pd(PPh}_3)_4, \text{POT, K}_2\text{CO}_3} \text{Ar}^1\text{-Ar}^2$
<b>C</b>	1	1a	3	$\text{R}^1\text{-NO}_2 \xrightarrow[\text{EtOAc or MeOH}]{\text{H}_2, \text{Pd/C}} \text{R}^1\text{-NH}_2$ <p style="text-align: center;">or</p> $\text{R}^1\text{-CH=CH-R}^2 \xrightarrow[\text{EtOAc or MeOH}]{\text{H}_2, \text{Pd/C}} \text{R}^1\text{-CH}_2\text{-CH}_2\text{-R}^2$
<b>D</b>	1	1a	4	$\text{X-CH}_2\text{-R}^3 + \text{R}^1\text{-}\overset{\text{H}}{\underset{\text{R}^2}{\text{N}}} \xrightarrow[\text{or K}_2\text{CO}_3, \text{DMF, rt}]{\text{K}_2\text{CO}_3, \text{DME; rt}} \text{R}^1\text{-}\overset{\text{R}^2}{\underset{\text{CH}_2\text{-R}^3}{\text{N}}}$

Proc	Sc	Ex	Step	Reaction Conditions
E	1	1a	5	$\text{R}^1-\text{C}(=\text{O})\text{OR} \xrightarrow[110^\circ\text{C}]{2\text{N HCl}} \text{R}^1-\text{C}(=\text{O})\text{OH}$
F	1	1a	6	$\text{R}^1-\text{C}(=\text{O})\text{OH} + \text{Ar}^1-\text{NH}_2 \xrightarrow[\text{or BOP, DMAP, Pyridine}]{\text{BOP, Pyridine or BOP, Et}_3\text{N, Pyridine}} \text{R}^1-\text{C}(=\text{O})\text{NH}-\text{Ar}^1$
G	1	1a	7	$\text{Ar}^1-\text{N}(\text{H})-\text{Boc} \xrightarrow{\text{TFA, DCM}} \text{Ar}^1-\text{NH}_2$
H	2	2a	2	$\text{Ar}^1-\text{X} + \text{CH}_2=\text{CH}-\text{C}(=\text{O})\text{OR}^2 \xrightarrow[\text{DIPEA, DMF, } 120^\circ\text{C}]{\text{Pd}_2(\text{dba})_2, \text{POT}} \text{Ar}^1-\text{CH}=\text{CH}-\text{C}(=\text{O})\text{OR}^2$
I	2	2a	3	$\text{R}^1-\text{C}(=\text{O})\text{OtBu} \xrightarrow{\text{TFA, DCM}} \text{R}^1-\text{C}(=\text{O})\text{OH}$
J	37	37a	1	$\text{R}^1-\text{NH}-\text{R}^2 + \text{X}-\text{Ar}^1 \xrightarrow[\text{or DMSO, } 90-130^\circ\text{C or K}_2\text{CO}_3, \text{DMSO, } 90-130^\circ\text{C}]{90-130^\circ\text{C}} \text{R}^1-\text{N}(\text{R}^2)-\text{Ar}^1$
K	6	6a	1	$\text{R}^1-\text{C}(=\text{O})\text{Cl} + \text{R}^2-\text{NH}_2 \xrightarrow[\text{or Pyridine}]{\text{Et}_3\text{N, DCM}} \text{R}^1-\text{C}(=\text{O})\text{NH}-\text{R}^2$
L	6	6a	2	$\text{Br}-\text{CH}_2-\text{R}^3 + \text{R}^1-\text{N}(\text{H})-\text{R}^2 \xrightarrow[\text{DCM, Acetone}]{\text{K}_2\text{CO}_3, \text{NaI}} \text{R}^1-\text{N}(\text{R}^2)-\text{CH}_2-\text{R}^3$
M	10	10a	1	$\text{R}^1-\text{NH}-\text{R}^2 + \text{EtO}_2\text{C}-\text{C}_5\text{H}_3\text{N}_2-\text{SO}_2 \xrightarrow{\text{DME, rt}} \text{R}^1-\text{N}(\text{R}^2)-\text{C}_5\text{H}_3\text{N}_2-\text{CO}_2\text{Et}$
N	29	29a	1	$\text{R}^1-\text{C}(=\text{O})\text{OH} + \text{Ar}^1-\text{NH}_2 \xrightarrow[\text{DMF}]{\text{BOP, Et}_3\text{N}} \text{R}^1-\text{C}(=\text{O})\text{NH}-\text{Ar}^1$
O	34	34b	3	$\text{R}^1-\text{O}-\text{Ac} \xrightarrow[\text{or NH}_3, \text{MeOH}]{\text{Et}_3\text{N, MeOH}} \text{R}^1-\text{OH}$
P	37	37a	3	$\text{R}^1-\text{C}(=\text{O})\text{OR}^2 \xrightarrow[\text{MeOH, THF, H}_2\text{O}]{\text{LiOH}\cdot\text{H}_2\text{O}} \text{R}^1-\text{C}(=\text{O})\text{OH}$ <p>The use of NaOH or KOH instead LiOH.H<sub>2</sub>O is also considered.</p>

Proc	Sc	Ex	Step	Reaction Conditions
<b>Q</b>	41	41a	1	$\text{R}^1\text{-C}_6\text{H}_3\text{(OH)-CHO} \xrightarrow[\text{K}_2\text{CO}_3/\text{DMF}, 80^\circ\text{C}]{\text{Methyl 2-bromoacetate}} \text{R}^1\text{-C}_6\text{H}_3\text{(O)-CH=CH-C(=O)OMe}$
<b>R</b>	41	41a	2	$\text{R}^1\text{-O-Bn or R}^1\text{-N(H)-Cbz} \xrightarrow[\text{MeOH}]{\text{H}_2, \text{Pd/C 10\%}} \text{R}^1\text{-OH or R}^1\text{-NH}_2$
<b>S</b>	41	41a	3	$\text{R}^2\text{-N(R}^1\text{)-CH}_2\text{CH}_2\text{Cl} + \text{HO-Ar}^1 \xrightarrow[\text{DMF, acetone}]{\text{K}_2\text{CO}_3} \text{R}^2\text{-N(R}^1\text{)-CH}_2\text{CH}_2\text{O-Ar}^1$
<b>T</b>	42	42a	1	$\text{R}^1\text{-NH}_2 \xrightarrow[\text{DCM, Na}_2\text{CO}_3, 0^\circ\text{C to rt}]{\text{CBzCl}} \text{R}^1\text{-NHCBz}$
<b>U</b>	42	42a	5a	$\text{R}^1\text{-NH}_2 \xrightarrow[\text{Et}_3\text{N, DCM}]{\text{R}^2\text{SO}_2\text{Cl or (R}^2\text{SO}_2)_2\text{O}} \text{R}^1\text{-N(H)-SO}_2\text{-R}^2$
<b>V</b>	42	42b	5b	$\text{R}^1\text{-OH} \xrightarrow[\text{Pyridine}]{\text{Ac}_2\text{O or AcCl}} \text{R}^1\text{-O-Ac}$
<b>W</b>	42	42b	6b	$\text{R}^1\text{-N(H)-Boc} \xrightarrow[\text{Dioxane or DCM}]{\text{HCl 4M in Dioxane}} \text{R}^1\text{-NH}_2$
<b>X</b>	33	33a	1	$\text{R}^1\text{-O-C(=O)-N=C-N-C}_6\text{H}_4\text{-C(=O)OEt} \xrightarrow[\text{THF, rt}]{\text{R}^1\text{OH}} \text{R}^1\text{-O-C(=O)-NH-C}_6\text{H}_4\text{-C(=O)OEt}$
<b>Y</b>	45	45a	2	$\text{Ar}^1\text{-CH}_2\text{-X} \xrightarrow[\text{2) Methyl propiolate, CuSO}_4, \text{Na Ascorbate, H}_2\text{O}]{\text{1) NaN}_3/\text{DMSO}} \text{Ar}^1\text{-CH}_2\text{-N=N-C}_5\text{H}_3\text{(N)-C(=O)OMe}$
<b>Z</b>	7	7a	2	$\text{R}^3\text{-CHO} + \text{HN(R}^1\text{)-R}^2 \xrightarrow[\text{DME}]{\text{PhSiH}_3, \text{BuSnCl}_2} \text{R}^3\text{-CH}_2\text{-N(R}^1\text{)-R}^2$
<b>AA</b>	25	25a	1	$\text{HN(R}^1\text{)-R}^2 \xrightarrow[\text{2. R}^3\text{OH}]{\text{1. CDI, pyridine; rt}} \text{R}^1\text{-N(R}^2\text{)-C(=O)OR}^3$
<b>BB</b>	24	24a	2	$\text{HN(R}^1\text{)-R}^2 \xrightarrow[\text{2. R}^3\text{OH}]{\text{1. Triphosgene, DCM}} \text{R}^1\text{-N(R}^2\text{)-C(=O)OR}^3$

Proc	Sc	Ex	Step	Reaction Conditions
CC	7	7a	1	$\text{R}^1-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH} \xrightarrow[\text{or oxalyl chloride, Et}_3\text{N, DCM}]{\text{SOCl}_2, \text{DMF}_{\text{cat.}}, \text{DCE}} \text{R}^1-\overset{\text{O}}{\parallel}{\text{C}}-\text{Cl}$
DD	20	20a	7	$\text{R}^3-\text{CHO} + \text{H}\overset{\text{R}^2}{\underset{\text{R}^1}{\text{N}}} \xrightarrow[\text{DCE}]{\text{NaHB(OAc)}_3} \text{R}^3-\text{CH}_2-\overset{\text{R}^2}{\underset{\text{R}^1}{\text{N}}}$
EE	10	10a	2	$\text{R}^1-\text{S}-\text{Ar} \xrightarrow[\text{DCM}]{m\text{CPBA}} \text{R}^1-\overset{\text{O}_2}{\underset{\text{O}}{\text{S}}}-\text{Ar}$
FF	14	14a	4	$\text{Ar}^1-\text{NO}_2 \xrightarrow[\text{THF, MeOH, H}_2\text{O}]{\text{SnCl}_2, \text{NH}_4\text{OAc}} \text{Ar}^1-\text{NH}_2$
GG	44	44	1	$\text{R}^1-\text{OH} + \text{X}-\text{R}^2 \xrightarrow[\text{THF or DMF}]{\text{NaH}} \text{R}^1-\text{O}-\text{R}^2$
HH	28	28a	3	$\text{HO}-\text{R}^1 + \text{H}\overset{\text{R}^2}{\underset{\text{R}^3}{\text{N}}} \xrightarrow[\text{THF}]{\text{DEAD, PPh}_3} \text{R}^1-\overset{\text{R}^3}{\underset{\text{R}^2}{\text{N}}}$ $\text{HO}-\text{R}^1 + \text{HO}-\text{R}^2 \xrightarrow[\text{THF}]{\text{DEAD, PPh}_3} \text{R}^1-\text{O}-\text{R}^2$

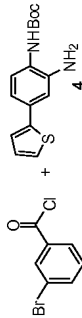
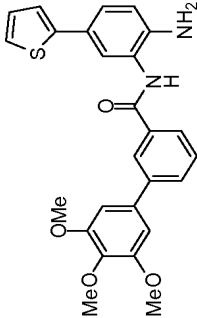
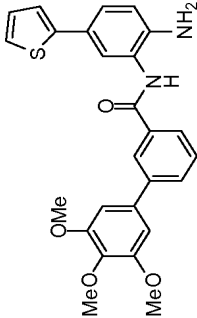
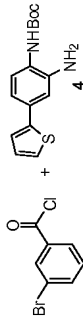
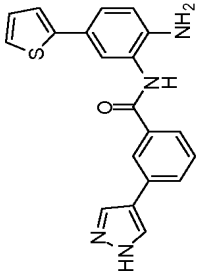
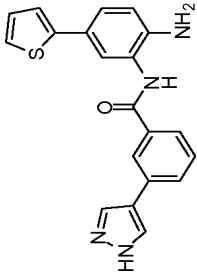
[1060]  $\text{Ar}^1, \text{Ar}^2, \text{Ar}^3$  = Can be a clinical appropriate moiety for this reaction. Those included but are not limited to aryl or heteroaryl, alkenyl and alkynyl.

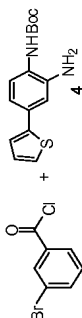
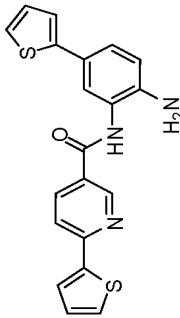
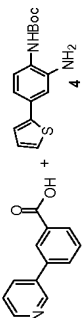
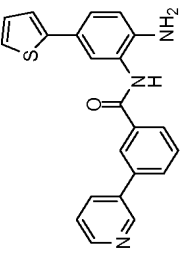
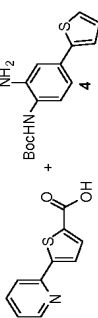
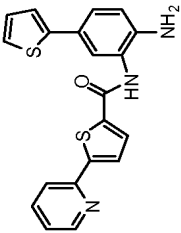
[1061]  $\text{R}^1, \text{R}^2, \text{R}^3$  = Can be a clinical appropriate moiety for this reaction. Those included but are not limited to aryl, heteroaryl, alkyl, heterocyclyl, and cycloalkyl.

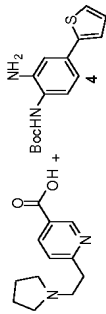
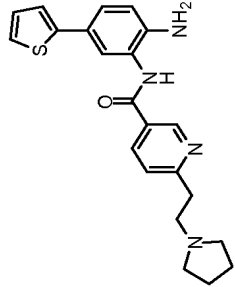
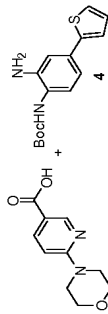
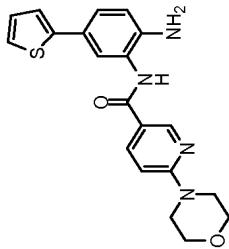
[1062] X = halogen

[1063] The compounds **56-58**, **61-72**, **320** and **372-389** described in this invention are prepared starting from the corresponding starting material and following the preparative sequence (general procedure **A** to **O**) indicated in Table 21.

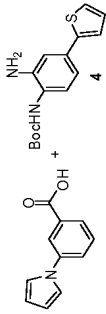
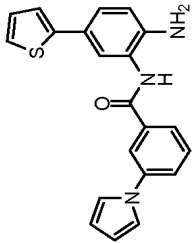
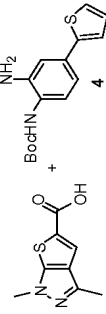
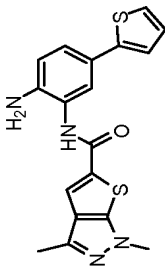
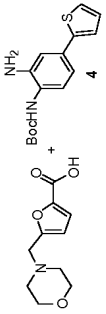
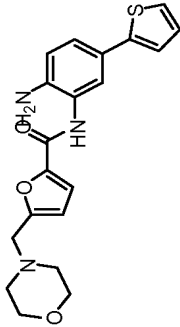
Table 22: Characterization and preparative sequence of compounds synthesized

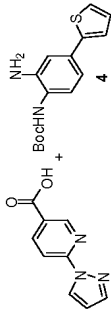
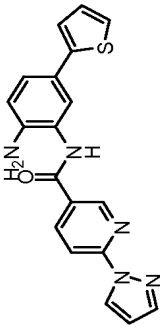
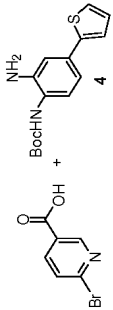
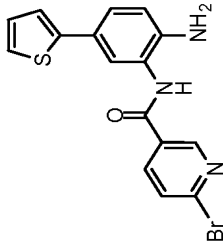
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
4a	56	 		<i>N</i> -(2-Amino-5-(thiophen-2-yl)phenyl)-3-(4-methoxy-2,6-dimethoxyphenyl)-3-carboxamide 2,2,2-trifluoroacetate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.82 (s, 1H), 8.24 (s, 1H), 7.91 (dd, J=21.1, 7.6 Hz, 2H), 7.58 (t, J=7.8 Hz, 1H), 7.49 (s, 1H), 7.35 (d, J=5.1 Hz, 1H), 7.31 (dd, J=8.2, 2.0 Hz, 1H), 7.24 (d, J=3.3 Hz, 1H), 7.05 to 7.03 (m, 1H), 7.01 (s, 2H), 6.81 (d, J=8.4 Hz, 1H), 3.88 (s, 6H), 3.70 (s, 3H). LRMS: calc. 460.2, found 461.2 (MH) <sup>+</sup> .	K, B, G
4b	57	 		<i>N</i> -(2-amino-5-(thiophen-2-yl)phenyl)-3-(1H-pyrazol-4-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.69 (s, 1H), 8.14 (s, 1H), 8.12 to 8.07 (m, 1H), 7.71 (t, J=9.0 Hz, 2H), 7.40 (t, J=7.6 Hz, 2H), 7.28 to 7.27 (m, 1H), 7.23 (dd, J=8.4, 2.0 Hz, 1H), 7.17 (d, J=2.3 Hz, 1H), 7.01 (m, 1H), 6.97 (dd, J=5.1, 3.5 Hz, 1H), 6.75 (d, J=8.2 Hz, 1H). LRMS: calc. 360.1, found 361.1.	K, B, G

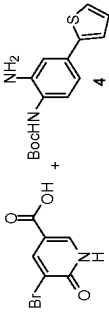
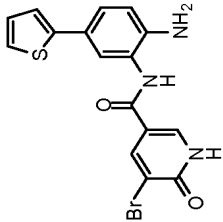
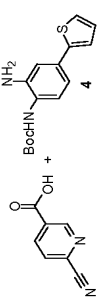
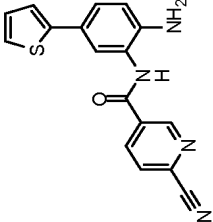
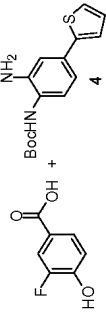
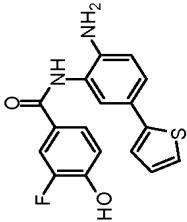
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
4c	58			N-(2-amino-5-(thiophen-2-yl)phenyl)-6-(thiophen-2-yl)nicotinamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.00 (s, 1H), 9.05 (dd, J=14.4, 2.4 Hz, 2H), 8.56 (t, J=2.0 Hz, 1H), 7.77 (dd, J=3.6, 1.2 Hz, 1H), 7.71 (dd, J=5.2, 1.2 Hz, 1H), 7.47 (d, J=2.4 Hz, 1H), 7.34 (dd, J=5.2, 1.2 Hz, 1H), 7.31 (dd, J=8.4, 2.4 Hz, 1H), 7.25-7.22 (m, 2H), 7.03 (dd, J=4.8, 3.2 Hz, 1H), 6.80 (d, J=8.0 Hz, 1H), 5.32 (s, 2H). LRMS: calc. 376.5, found 377.9	K, B, G
5a	61			N-(2-Amino-5-(thiophen-2-yl)phenyl)-3-(pyridin-3-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.99 (s, 1H), 9.13 (s, 1H), 8.72 (d, J= 5.1 Hz, 1H), 8.47 (s, J= 7.6 Hz, 1H), 8.41 (s, 1H), 8.03 (dd, J= 21.7 Hz, 7 Hz, 2H), 7.76 (t, J= 5.1 Hz, 1H), 7.69 (t, J= 7.6 Hz, 1H), 7.51 (s, 1H), 7.39 to 7.35 (m, 2H), 7.29 (d, J= 2.5 Hz, 1H), 7.07 to 7.05 (m, 1H), 6.90 (d, J= 8.2 Hz, 1H).	F, G
5b	62			N-(2-amino-5-(thiophen-2-yl)phenyl)-5-(pyridin-2-yl)thiophene-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.80 (s, 1H), 8.57 (s, 1H), 7.99 (s, 2H), 7.87 (s, 2H), 7.44 (s, 1H), 7.34 to 7.25 (m, 4H), 7.04 (s, 1H), 6.81 (s, 1H), 5.21 (s, 2H). LRMS: calc. 337.1, found 378.1.	F, G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
5c	63			N-(2-amino-5-(thiophen-2-yl)phenyl)-6-(2-(pyrrolidin-1-yl)ethyl)nicotinamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.81 (s, 1H), 9.04 (d, J= 1.8 Hz, 1H), 8.23 (d, J= 8.2 Hz, 1H), 7.45 to 7.43 (m, 2H), 7.34 (dd, J= 5.1, 1.2 Hz, 1H), 7.29 (dd, J= 8.2, 2.2 Hz, 1H), 7.23 (dd, J= 3.5, 0.98 Hz, 1H), 7.03 (dd, J= 5.1, 3.7 Hz, 1H), 6.79 (d, J= 8.2 Hz, 1H), 5.22 (s, 2H), 2.98 (m, 2H), 2.82 (m, 1H), 1.67 (m, 4H), 1.26-1.22 (m, 3H). LRMS: calc. 392.2, found 393.2.	F, G
5d	64			N-(2-amino-5-(thiophen-2-yl)phenyl)-6-morpholinomycinamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.52 (s, 1H), 8.75 (s, J= 2.3 Hz, 1H), 8.10 (dd, J= 9.2, 2.5 Hz, 1H), 7.43 (d, J= 2.0 Hz, 1H), 7.33 (dd, J= 5.1, 1.2 Hz, 1H), 7.22 (dd, J= 3.5, 1.2 Hz, 1H), 7.03 (dd, J= 5.1, 3.5 Hz, 1H), 6.90 (d, J= 9.0 Hz, 1H), 6.78 (d, J= 8.4 Hz, 1H), 5.14 (s, 2H), 3.70 (t, J= 4.8 Hz, 4H), 3.58 (t, J= 4.8 Hz, 4H). LRMS: calc. 380.1, found 381.1.	F, G

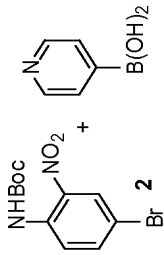
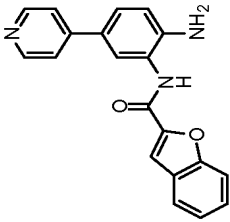
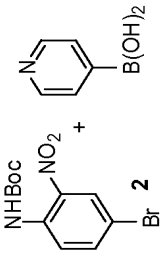
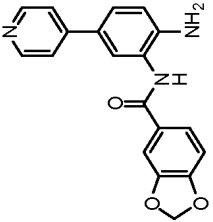
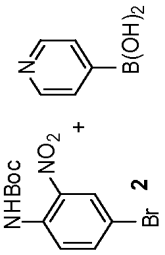
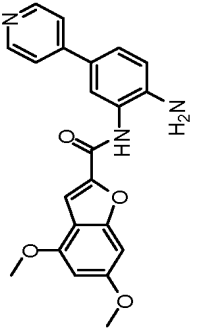


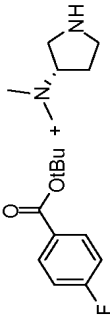
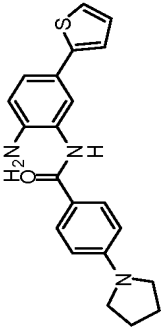
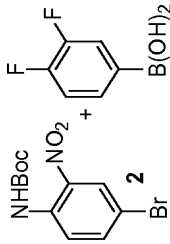
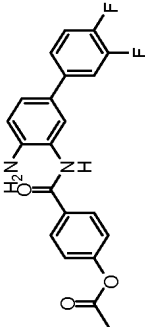
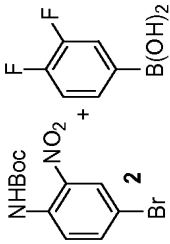
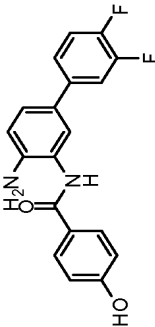
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
5e	65			N-(2-amino-5-(thiophen-2-yl)phenyl)-2-(1H-pyrrol-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.85 (s, 1H), 8.17 (s, 1H), 7.80 (dd, J= 15.5, 7.4 Hz, 2H), 7.58 (t, J= 7.8 Hz, 1H), 7.48 (t, J= 2.2 Hz, 3H), 7.35 (dd, J= 5.1, 1.2 Hz, 1H), 7.31 (dd, J= 8.4, 2.2 Hz, 1H), 7.25 (d, J= 3.5 Hz, 1H), 7.05-7.03 (m, 1H), 6.82 (d, J= 8.2 Hz, 1H), 6.30 (t, J= 2.2 Hz, 1H). LRMS: calc. 359.1, found 360.1.	F, G
5f	66			N-(2-amino-5-(thiophen-2-yl)phenyl)-1,3-dimethyl-1H-thieno[2,3-c]pyrazole-5-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.75 (s, 1H), 8.03 (s, 1H), 7.45 (d, J= 2.2 Hz, 1H), 7.36 (dd, J= 4.9, 0.98 Hz, 1H), 7.30 (dd, J= 8.4, 2.3 Hz, 1H), 7.25 (dd, J= 3.5, 0.98 Hz, 1H), 7.05 (dd, J= 5.1, 3.5 Hz, 1H), 6.81 (d, J= 8.4 Hz, 1H), 5.21 (s, 2H), 3.89 (s, 3H), 2.39 (s, 3H). LRMS: calc. 368.1, found 369.0.	F, G
5g	67			N-(2-amino-5-(thiophen-2-yl)phenyl)-5-(morpholino(methyl)furan-2-yl)carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.57 (s, 1H), 7.40 (d, J=2.2 Hz, 1H), 7.34 (dd, J=5.1, 1.2 Hz, 1H), 7.27 (dd, J=8.4, 1.2 Hz, 1H), 7.26 (d, J=3.3 Hz, 1H), 7.22 (dd, J=3.7, 1.2 Hz, 1H), 7.03 (dd, J=5.1, 3.5 Hz, 1H), 6.78 (d, J=8.4 Hz, 1H), 5.12 (s, 2H), 3.58-3.54 (m, 6H), 2.42-2.39 (m, 4H). LRMS: calc. 383.5, found 384.1.	F, G

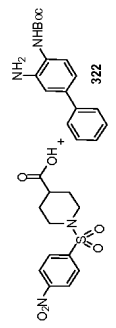
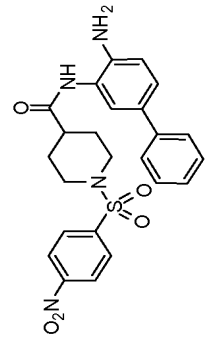
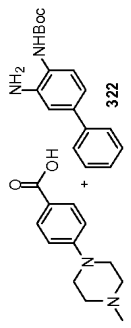
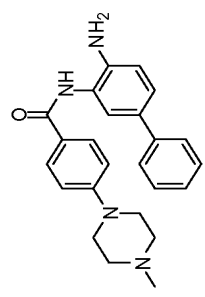
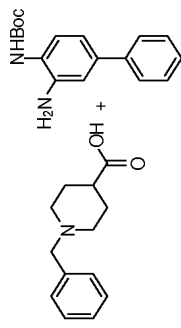
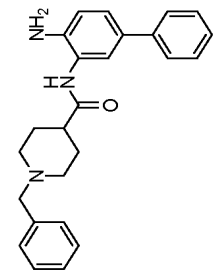
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
<b>5h</b>	<b>68</b>			N-(2-amino-5-(thiophen-2-yl)phenyl)-6-(1H-pyrazol-1-yl)nicotinamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.95 (bs, 1H), 9.07 (d, J=2.0 Hz, 1H), 8.73 (d, J=2.8 Hz, 1H), 8.55 (dd, J=8.8 Hz, J=2.4 Hz, 1H), 8.05 (d, J=8.4 Hz, 1H), 7.91 (m, 1H), 7.49 (d, J=2.4 Hz, 1H), 7.36 (dd, J=5.0, 1.0 Hz, 1H), 7.32 (dd, J=8.4, 2.4 Hz, 1H), 7.26 (dd, J=3.2, 1.2 Hz, 1H), 7.05 (dd, J=5.2, 3.6 Hz, 1H), 6.81 (d, J=8.4 Hz, 1H), 6.65 (dd, J=2.6, 1.8 Hz, 1H), 5.29 (s, 2H). LRMS: calc. 361.1, found 362.1.	F, G
<b>5i</b>	<b>69</b>			N-(2-amino-5-(thiophen-2-yl)phenyl)-6-bromonicotinamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.95 (s, 1H), 8.96 (d, J=2.0 Hz, 1H), 8.27 (dd, J=8.4, 2.4 Hz, 1H), 7.84 (d, J=8.4 Hz, 1H), 7.45 (d, J=2.0 Hz, 1H), 7.35 (dd, J=5.2, 1.2 Hz, 1H), 7.32 (dd, J=8.4, 2.0 Hz, 1H), 7.24 (dd, J=3.6, 0.8 Hz, 1H), 7.05 (dd, J=5.2, 3.6 Hz, 1H), 6.80 (d, J=8.0 Hz, 1H), 5.30 (s, 2H). LRMS: calc. 373.0, found 373.9.	F, G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
5j	70			N-(2-amino-5-(thiophen-2-yl)phenyl)-5-bromo-6-oxo-1,6-dihydropyridine-3-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 12.29 (s, 1H), 9.52 (s, 1H), 8.43 (d, J=2.4 Hz, 1H), 8.21 (d, J=2.8 Hz, 1H), 8.36 (d, J=2.0 Hz, 1H), 7.33 (dd, J=5.2, 1.2 Hz, 1H), 7.27 (dd, J=8.4, 2.0 Hz, 1H), 7.21 (dd, J=3.6, 0.8 Hz, 1H), 7.02 (dd, J=5.2, 3.6 Hz, 1H), 6.75 (d, J=8.4 Hz, 1H), 5.21 (s, 2H). LRMS: calc. 390.3, found 391.8.	F, G
5k	71			N-(2-amino-5-(thiophen-2-yl)phenyl)-6-cyanonicotinamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.07 (s, 1H), 9.26 (d, J=1.6 Hz, 1H), 8.22 (t, 7.6 Hz, 1H), 7.44 (d, J=2.4 Hz, 1H), 7.33 (dd, J=5.2, 0.8 Hz, 1H), 7.30 (dd, J=8.0, 2.0 Hz), 7.22 (dd, J=3.6, 1.2 Hz, 1H), 7.02 (dd, J=5.2, 3.6 Hz, 1H), 7.78 (d, J=8.4 Hz, 1H). LRMS: calc. 320.4, found 321.0.	F, G
5l	72			N-(2-amino-5-(thiophen-2-yl)phenyl)-3-fluoro-4-hydroxybenzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.60 (s, 1H), 7.82 (d, J=12.1 Hz, 1H), 7.71 (d, J=8.4 Hz, 1H), 7.43 (d, J=2.2 Hz, 1H), 7.35 (dd, J=5.1, 1.2 Hz, 1H), 7.29 (dd, J=8.4, 2.2 Hz, 1H), 7.24 (dd, J=3.5, 1.2 Hz, 1H), 7.06-7.04 (m, 2H), 6.80 (d, J=8.4 Hz, 1H), 5.15 (s, 2H). LRMS: calc. 328.1, found 329.0.	F, G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
5m	372			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(piperidin-1-yl)benzamide	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ (ppm): 8.21 (s, 1H), 7.78 (d, J=8.1 Hz, 2H), 7.49 (s, 1H), 7.12 (m, 2H), 6.91 (m, 3H), 6.80 (d, J=8.2 Hz, 1H), 3.21 (m, 4H), 1.63 (m, 4H), 1.58 (m, 2H). LRMS: calc. 377.5, found 378.1 (MH) <sup>+</sup> .	F, G
5n	373			N-(2-amino-5-(thiazol-2-yl)phenyl)-4-(4-methylpiperazin-1-yl)benzamide	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.50(s, 1H), 7.89(d, 2H), 7.79(dd, 1H), 7.76(d, 1H), 7.57-7.54(m, 2H), 7.00(d, 1H), 6.83(d, 1H), 5.43(s, 2H), 3.28(t, 4H), 2.45(t, 4H), 2.23(s, 3H) LRMS: calc. 393.2, found 394.2 (MH) <sup>+</sup>	B, C, F, G
5o	374			N-(2-amino-5-(pyridin-4-yl)phenyl)-3-methoxybenzamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) □ (ppm): 8.46 (d, J=6.3 Hz, 2H), 7.66-7.63 (m, 3H), 7.60-7.52 (m, 3H), 7.43 (t, J=8.0 Hz, 1H), 7.16-7.13 (m, 1H), 6.99 (d, J=8.4 Hz, 1H), 3.87 (s, 3H). LRMS: calc. 319.2, found 320.3 (MH) <sup>+</sup>	B, C, F, G
5p	375			N-(2-amino-5-(pyridin-4-yl)phenyl)-4-(dimethylamino)benzamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) □ (ppm): 8.56-8.40 (m, 2H), 7.90 (d, J=9.0 Hz, 2H), 7.69-7.65 (m, 3H), 7.53 (dd, J=8.4, 2.2 Hz, 1H), 6.98 (d, J=8.4 Hz, 1H), 6.79 (d, J=9.2 Hz, 2H), 3.05 (s, 6H). LRMS: calc. 332.2, found 333.3 (MH) <sup>+</sup> .	B, C, F, G

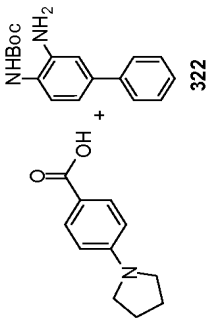
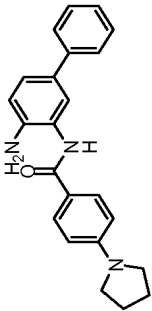
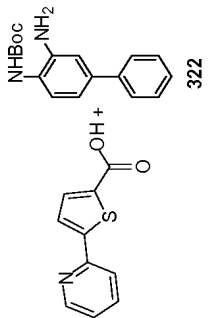
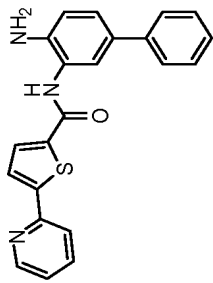
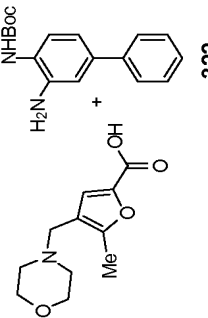
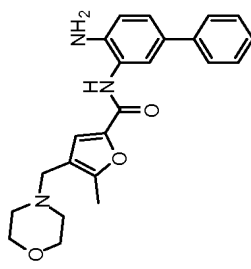
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
5q	376			N-(2-amino-5-(pyridin-4-yl)phenyl)benzofuran-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) □ (ppm): 8.46-8.43 (m, 2H), 7.75-7.70 (m, 2H), 7.65-7.61 (m, 4H), 7.54-7.45 (m, 2H), 7.35-7.31 (m, 1H), 6.98 (d, J=8.4 Hz, 1H).LRMS: calc. 329.1, found 330.2 (MH) <sup>+</sup>	B, C, F, G
5r	377			N-(2-amino-5-(pyridin-4-yl)phenyl)benzoxazole-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.59 (s, 1H), 8.50 (s, 2H), 7.64-7.48 (m, 6H), 7.04 (d, J=8.2 Hz, 1H), 6.87 (d, J=8.0 Hz, 1H), 6.12 (s, 2H), 5.35 (s, 2H).LRMS: calc. 333.1, found 334.3 (MH) <sup>+</sup>	B, C, F, G
5s	378			N-(2-amino-5-(pyridin-4-yl)phenyl)-4,6-dimethoxybenzofuran-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) □ (ppm): 8.48-8.46 (m, 2H), 7.71 (d, J=2.1 Hz, 1H), 7.67-7.65 (m, 2H), 7.59 (s, 1H), 7.55 (dd, J=8.6, 2.4 Hz, 1H), 6.99 (d, J=8.6 Hz, 1H), 6.81 - 6.80 (m, 1H), 6.45 (d, J=2.0 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H).LRMS: calc. 389.1, found 390.2 (MH) <sup>+</sup>	B, C, F, G

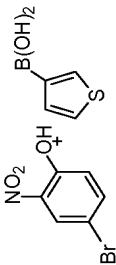
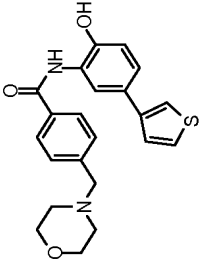
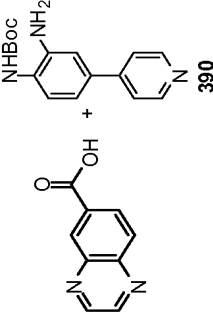
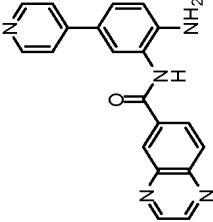
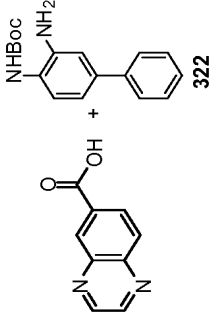
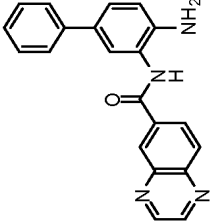
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
8k	379			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(pyrrolidin-1-yl)benzamide	<sup>1</sup> H NMR (Acetone-d <sub>6</sub> ) □ (ppm): 8.92 (s, 1H), 7.94 (d, J=9.0 Hz, 2H), 7.63 (d, J=2.2 Hz, 1H), 7.31 (dd, J=8.4, 2.2 Hz, 1H), 7.28 (dd, J=5.1, 1.2 Hz, 1H), 7.23 (dd, J=3.5, 1.0 Hz, 1H), 7.04 (dd, J=5.1, 3.5 Hz, 1H), 6.90 (d, J=8.2 Hz, 1H), 6.61 (d, J=8.8 Hz, 2H), 4.80 (bs, 2H), 3.38-3.34 (m, 4H), 2.06-2.03 (m, 4H). LRMS: calc. 363.5, found 364.0.	J, I, F, G
34m	380			4-(4-amino-3',4'-difluorobiphenyl-3-yl)-3-ylcarbamoyl phenyl acetate	<sup>1</sup> H NMR (Acetone-d <sub>6</sub> ) □ (ppm): 9.18 (bs, 1H), 8.11 (d, J=8.6 Hz, 2H), 7.66 (t, J=2.3 Hz, 1H), 7.52 (ddd, J=12.3, 7.6, 2.2 Hz, 1H), 7.43-7.39 (m, 1H), 7.36 (dd, J=8.4, 2.3 Hz, 2H), 7.28 (d, J=8.6 Hz, 2H), 6.97 (d, J=8.4 Hz, 1H), 4.93 (bs, 2H), 2.33 (s, 3H). LRMS: calc. 382.4, found 383.0.	B, C, F, G
34n	381			N-(4-amino-3',4'-difluorobiphenyl-3-yl)-4-hydroxybenzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.07 (s, 1H), 9.51 (s, 1H), 7.86 (d, J=8.8 Hz, 2H), 7.58 (ddd, J=12.7, 7.8, 2.2 Hz, 1H), 7.49 (d, J=2.3 Hz, 1H), 7.45-7.35 (m, 2H), 7.31 (dd, J=8.4, 2.2 Hz, 1H), 6.83 (d, J=8.8 Hz, 2H), 6.82 (d, J=8.4 Hz, 1H), 5.12 (s, 2H). LRMS: calc. 340.3, found 341.0.	B, C, F, G, O

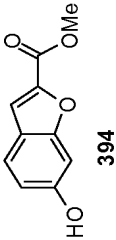
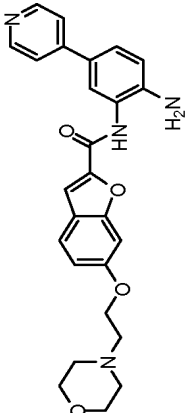
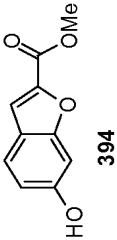
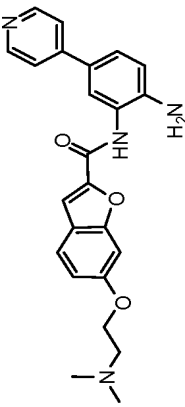
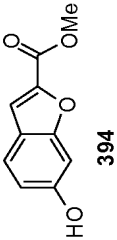
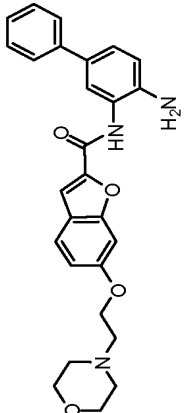
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
36	320			N-(4-aminobiphenyl-3-yl)-1-(4-nitrophenyl)piperidine-4-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.14 (s, 1H), 8.46 (d, J=8.8 Hz, 2H), 8.05 (d, J=8.8 Hz, 2H), 7.48 (m, 3H), 7.37 (t, J=7.6 Hz, 2H), 7.23 (m, 2H), 6.78 (d, J=8.0 Hz, 1H), 4.98 (s, 2H), 3.72 (d, J=12.0 Hz, 2H), 2.38-2.51 (m, 3H), 1.94 (dd, J=14.2, 3.0 Hz, 2H), 1.63-1.73 (m, 2H). LRMS: calc. 480.2, found 481.0 (MH) <sup>+</sup> .	N, G
	382			N-(4-aminobiphenyl-3-yl)-1-(4-methylpiperazin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.52 (s, 1H), 7.89 (d, J=9.2 Hz, 2H), 7.55 (dd, J=8.4 Hz, 2H), 7.51 (m, 1H), 7.39 (t, J=8.0 Hz, 2H), 7.31 (dd, J=8.4, 2.4 Hz, 1H), 7.24 (tt, J=7.4, 1.2 Hz, 1H), 7.01 (d, J=9.2 Hz, 2H), 6.86 (d, J=8.4 Hz, 1H), 5.04 (bs, 2H), 3.28 (t, J=5.0 Hz, 4H), 2.45 (t, J=5.0 Hz, 4H), 2.23 (s, 3H). LRMS: calc. 386.2, found 387.2 (MH) <sup>+</sup> .	F, G
	383			N-(4-aminobiphenyl-3-yl)-1-benzylpiperidine-4-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) □ (ppm): 7.58-7.53 (m, 2H), 7.42-7.24 (m, 10H), 6.94 (d, J = 8.2 Hz, 1H), 3.59 (s, 2H), 3.09-3.00 (m, 2H), 2.56-2.45 (m, 1H), 2.22-2.12 (m, 2H), 2.00-1.90 (m, 4H). LRMS: calc. 385.5, found 386.5 (MH) <sup>+</sup> .	F, G

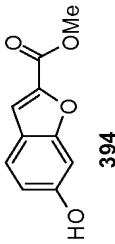
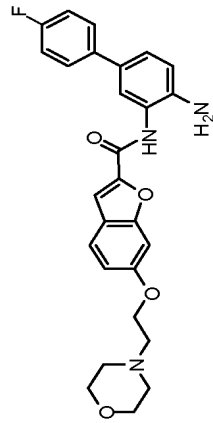
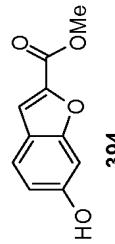
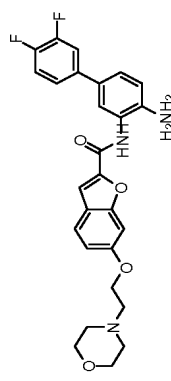
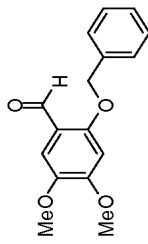
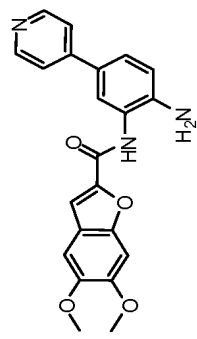
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	384			N-(4-aminobiphen-3-yl)-4-(4-methylpiperazin-1-yl)-3-(pyridin-3-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.96 (s, 1H), 8.23 (d, J=8.4 Hz, 2H), 7.86 (d, J=8.4 Hz, 2H), 7.55-7.50 (m, 3H), 7.40-7.32 (m, 3H), 7.23 (t, J=7.4 Hz, 1H), 6.85 (d, J=8.4 Hz, 1H), 5.17-5.14 (m, 2H), 2.96-2.88 (m, 4H), 2.38-2.35 (m, 4H), 2.13 (s, 3H). LRMS: calc. 450.2, found 451.2 (MH) <sup>+</sup> .	F, G
	385			N-(4-aminobiphen-3-yl)-4-(4-methylpiperazin-1-yl)-3-(pyridin-3-yl)benzamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) □ (ppm): 8.96 (d, J = 1.8 Hz, 1H), 8.60 (dd, J = 4.9, 1.7 Hz, 1H), 8.38 (t, J = 1.6 Hz, 1H), 8.28-8.23 (m, 1H), 8.15-8.09 (m, 1H), 7.98-7.93 (m, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.63-7.54 (m, 4H), 7.45-7.38 (m, 3H), 7.31-7.25 (m, 1H), 7.02 (d, J = 8.4 Hz, 1H). LRMS: calc. 365.4, found 366.4 (MH) <sup>+</sup> .	F, G

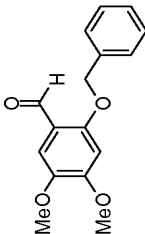
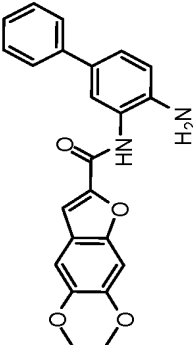
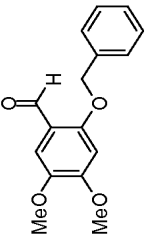
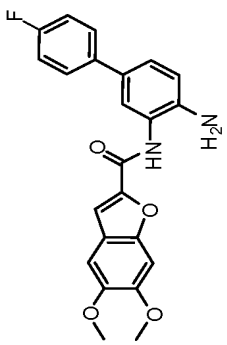
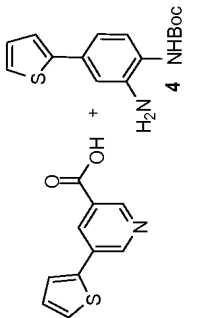
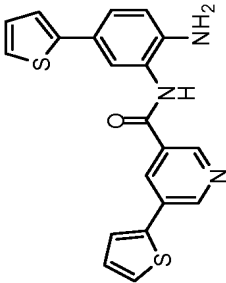


Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	386			N-((4-aminobiphenyl-3-yl)methyl)carbamate (pyrrolidin-1-yl)benzamide	Top of Form <sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.41 (s, 1H), 7.86 (d, J=8.8 Hz, 2H), 7.54 (d, J=8.4 Hz, 2H), 7.50 (d, J=2.2 Hz, 1H), 7.37 (d, J=7.4 Hz, 2H), 7.28 (dd, J=8.2, 2.1 Hz, 1H), 7.22 (t, J=7.4 Hz, 1H), 6.85 (d, J=8.2 Hz, 1H), 6.57 (d, J=8.8 Hz, 2H), 5.00 (d, J=9.6 Hz, 2H), 3.32-3.30 (m, 4H), 1.98-1.96 (m, 4H). LRMS: calc. 357.5, found 358.2 (MH) <sup>+</sup> .	F, G
	387			N-((4-aminobiphenyl-3-yl)methyl)carbamate (pyridin-2-yl)thiophene-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) □ (ppm): 8.60-8.55 (m, 1H), 7.98-7.86 (m, 3H), 7.78 (d, J = 4.1 Hz, 1H), 7.63-7.58 (m, 2H), 7.52 (d, J = 2.0 Hz, 1H), 7.44-7.34 (m, 4H), 7.31-7.24 (m, 1H), 7.01 (d, J = 8.2 Hz, 1H). LRMS: calc. 371.5, found, 372.2 (MH) <sup>+</sup> .	F, G
	388			N-((4-aminobiphenyl-3-yl)methyl)carbamate (morpholino)methylfuran-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) □ (ppm): 7.62-7.56 (m, 2H), 7.52 (d, J = 2.2 Hz, 1H), 7.44-7.37 (m, 3H), 7.30-7.23 (m, 2H), 6.99 (d, J = 8.2 Hz, 1H), 3.72 (t, J = 4.5 Hz, 4H), 3.44 (s, 2H), 2.57-2.50 (m, 4H), 2.44 (s, 3H). LRMS: calc. 391.5, found 392.2 (MH) <sup>+</sup> .	F, G

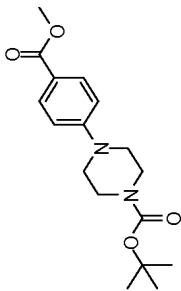
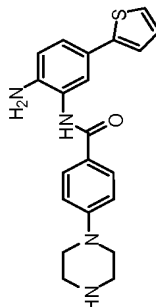
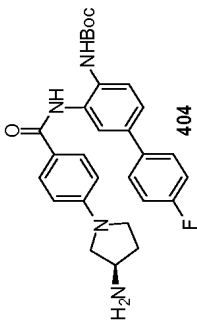
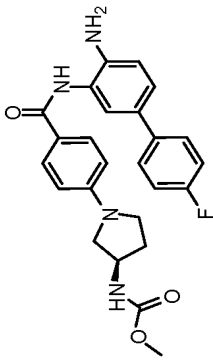
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	389			N-(2-hydroxy-5-(thiophen-3-yl)phenyl)-4-(morpholino methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.90 (s, 1H), 9.62 (s, 1H), 7.91 (m, 3H), 7.65 (m, 1H), 7.61 (m, 1H), 7.42 (m, 4H), 6.91 (d, J=8.1 Hz, 1H), 3.61 (m, H), 3.52 (s, 2H), 2.39 (m, 4H). LRMS: calc. 394.5, found 395.1 (MH) <sup>+</sup> .	B, C, F
	464			N-(2-amino-5-(pyridin-4-yl)phenyl)quinoline-6-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.99 (d, J=4.9 Hz, 2H), 8.79 (s, 1H), 8.48 (d, J=6.1 Hz, 2H), 8.44-8.41 (m, 1H), 8.24 (d, J=8.8 Hz, 1H), 7.74 (s, 1H), 7.68 (d, J=5.7 Hz, 2H), 7.58 (d, J=9.0 Hz, 1H), 7.01 (d, J=8.4 Hz, 1H). LRMS: calc. 341.2, found 342.4 (MH) <sup>+</sup> .	F, G
	465			N-(4-aminobiphen-3-yl)-3-quinoxalinyloxybenzamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 9.00-8.91 (m, 2H), 8.78 (d, J=2.0 Hz, 1H), 8.42 (dd, J=8.8 Hz, 2.0 Hz, 1H), 8.23 (d, J=8.8 Hz, 1H), 7.59-7.55 (m, 3H), 7.42-7.35 (m, 3H), 7.27-7.22 (m, 1H), 7.00 (d, J=8.2 Hz, 1H). LRMS: calc. 340.2, found 341.4 (MH) <sup>+</sup> .	F, G

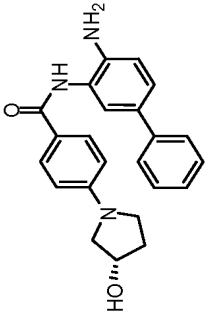
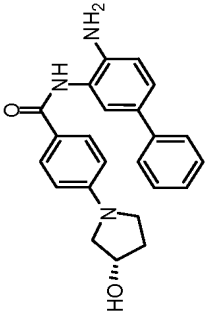
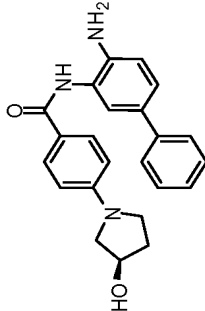
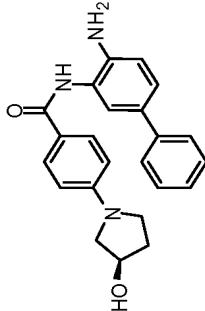
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	466			N-(2-amino-5-(pyridin-4-yl)phenyl)-6-(2-morpholinoethoxy)benzofuran-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.46 - 8.44 (m, 2H), 7.72 (d, J=2.2 Hz, 1H), 7.62-7.60 (m, 2H), 7.46 (dd, J=8.4, 2.3 Hz, 1H), 7.13-7.03 (m, 4H), 6.94 (d, J=8.4 Hz, 1H), 3.84 (s, 2H), 3.43 (s, 2H), 2.98-2.92 (m, 4H). LRMS: calc. 458.2, found 459.3 (MH) <sup>+</sup> .	S, P, F(with <b>390</b> ), G
	467			N-(2-amino-5-(pyridin-4-yl)phenyl)-6-(2-(dimethylamino)ethoxy)benzofuran-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.49 - 8.47 (m, 2H), 7.73 (d, J=2.2 Hz, 1H), 7.68-7.62 (m, 3H), 7.58-7.54 (m, 2H), 7.25 (d, J=1.7 Hz, 1H), 7.04-6.99 (m, 2H), 4.20 (t, J=5.3 Hz, 2H), 2.83 (t, J=5.5 Hz, 2H), 2.37 (s, 6H). LRMS: calc. 416.2, found, 417.2 (MH) <sup>+</sup> .	S, P, F(with <b>390</b> ), G
	468			N-(4-aminobiphenyl-3-yl)-6-(2-morpholinoethoxy)benzofuran-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 7.59 (d, J=8.6 Hz, 1H), 7.56-7.53 (m, 4H), 7.38-7.34 (m, 3H), 7.25-7.19 (m, 2H), 7.00-6.95 (m, 2H), 4.18 (t, J=5.5 Hz, 2H), 3.71 (t, J=4.7 Hz, 4H), 2.82 (t, J=5.5 Hz, 2H), 2.60 (t, J=4.5 Hz, 4H). LRMS: calc. 457.2, found 458.4 (MH) <sup>+</sup> .	S, P, F(with <b>322</b> ), G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	<b>469</b>			N-(4-amino-4'-(2-(4-(2-methoxy-3-((4-morpholin-2-ylmethoxy)methyl)phenoxy)phenyl)-6-(2-morpholinoethoxy)benzofuran-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 7.63 (d, J=8.8 Hz, 1H), 7.59-7.55 (m, 3H), 7.52 (d, J=2.2 Hz, 1H), 7.35 (dd, J=8.4, 2.4 Hz, 1H), 7.24 (d, J=2.0 Hz, 1H), 7.11 (t, J=8.8 Hz, 2H), 7.01 (dd, J=8.8, 2.3 Hz, 1H), 6.98 (d, J=8.0 Hz, 1H), 4.23 (t, J=5.5 Hz, 2H), 3.73 (t, J=4.7 Hz, 4H), 2.86 (t, J=5.5 Hz, 2H), 2.63 (t, J=4.7 Hz, 4H). LRMS: calc. 475.2, found 476.5 (MH) <sup>+</sup> .	S, P, F(with <b>402</b> ), G
	<b>470</b>			N-(4-amino-3',4'-difluorobiphenyl-3-yl)-6-(2-morpholinoethoxy)benzofuran-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 9.80 (s, 1H), 7.68 - 7.54 (m, 4H), 7.46 - 7.33 (m, 3H), 7.26 (d, J=1.6 Hz, 1H), 6.98 (dd, J=8.6, 2.1 Hz, 1H), 6.85 (d, J=8.4 Hz, 1H), 5.24 - 5.21 (m, 1H), 4.17 (t, J=5.7 Hz, 2H), 3.57 (t, J=4.7 Hz, 4H), 2.72 (t, J=5.6 Hz, 2H), 2.49 - 2.47 (m, 4H). LRMS: calc. 493.2, found 494.5 (MH) <sup>+</sup> .	S, P, F, G
	<b>471</b>			N-(2-amino-5-(pyridin-4-yl)phenyl)-5,6-dimethoxybenzofuran-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 9.77 (s, 1H), 8.50 (d, J=5.8 Hz, 2H), 7.69 (s, 1H), 7.63 (s, 1H), 7.58 (d, J=3.5 Hz, 2H), 6.88 (d, J=8.4 Hz, 1H), 5.41 (d, J=9.0 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H). LRMS: calc. 389.1, found 390.1 (MH) <sup>+</sup> .	R, Q, P, F(with <b>390</b> ), G

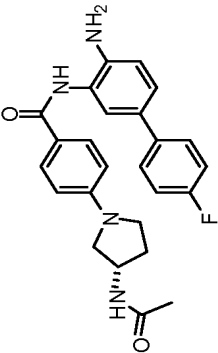
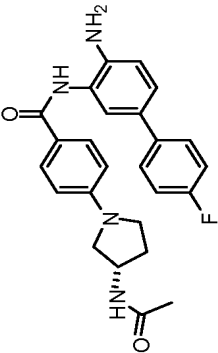
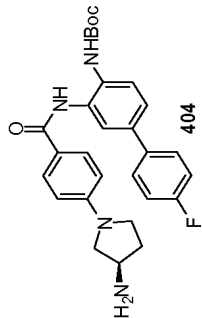
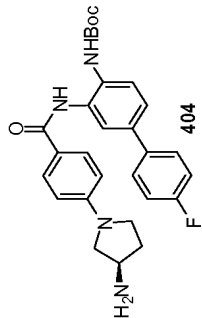
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	472			N-(4-aminobiphenyl-3-yl)-5,6-dimethoxybenzofuran-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 9.75 (s, 1H), 7.62 (s, 1H), 7.55 (d, J=7.2 Hz, 3H), 7.40-7.21 (m, 6H), 6.87 (d, J=8.4 Hz, 1H), 5.14 (br s, 2H), 3.85 (s, 3H), 3.81 (s, 3H). LRMS: calc. 388.1, found 389.1 (MH) <sup>+</sup> .	R, Q, P, F(with 322), G
	473			N-(4-amino-4'-fluorobiphenyl-3-yl)-5,6-dimethoxybenzofuran-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 9.75 (s, 1H), 7.62 - 7.50 (m, 4H), 7.31 - 7.27 (m, 3H), 7.21 (t, J=8.8 Hz, 2H), 6.86 (d, J=8.2 Hz, 1H), 5.14 (br s, 2H), 3.84 (s, 3H), 3.81 (s, 3H). LRMS: (calc.) 406.1 (found) 407.4 (MH) <sup>+</sup> .	R, Q, P, F(with 402), G
	474			N-(2-amino-5-(thiophen-2-yl)phenyl)-5-(thiophen-2-yl)nicotinamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 10.11 (s, 1H), 9.09 (d, J=2.4 Hz, 1H), 9.05 (d, J=1.6 Hz, 1H), 8.57 (t, J=2.0 Hz, 1H), 7.78 (dd, J=3.8, 1.0 Hz, 1H), 7.72 (dd, J=5.2, 1.2 Hz, 1H), 7.49 (d, J=2.4 Hz, 1H), 7.36 (dd, J=5.2, 1.2 Hz, 1H), 7.33 (dd, J=8.6, 2.2 Hz, 1H), 7.25 (m, 2H), 7.05 (dd, J=5.2, 3.6 Hz, 1H), 6.82 (d, J=8.4 Hz, 1H), 5.31 (s, 2H). LRMS: calc. 377.1, found 378.0 (MH) <sup>+</sup> .	N, W

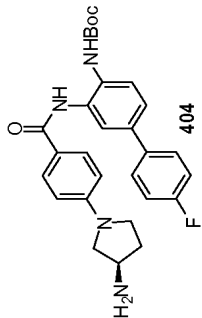
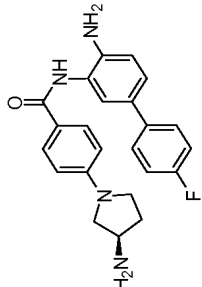
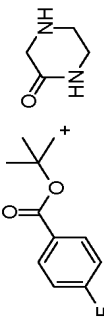
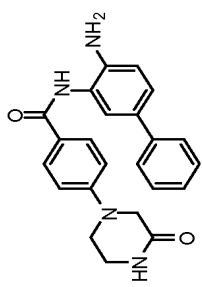
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	475			N-(2-amino-5-(thiophen-2-yl)phenyl)-5-(3-(dimethylamino)prop-1-ynyl)nicotinamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 9.94 (s, 1H), 9.08 (d, J=2.0 Hz, 1H), 8.81 (d, J=2.0 Hz, 1H), 8.43 (t, J=2.2 Hz, 1H), 7.46 (d, J=2.0 Hz, 1H), 7.36 (dd, J=5.2, 1.2 Hz, 1H), 7.31 (dd, J=8.4 Hz, 1H), 7.24 (dd, J=3.6, 1.2 Hz, 1H), 7.05 (dd, J=5.0, 3.4 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.30 (s, 2H), 3.54 (s, 2H), 2.28 (s, 6H), LRMS: calc. 376.1, found 377.0 (MH) <sup>+</sup> .	P, F(with 4), G
	476			N-(4-aminobiphen-1-yl)-4-(piperazin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 9.51 (s, 1H), 7.89 (d, J=9.2 Hz, 2H), 7.55 (dd, J=8.4, 1.2 Hz, 2H), 7.51 (d, J=2.4 Hz, 1H), 7.39 (t, J=7.8 Hz, 2H), 7.31 (dd, J=8.4, 2.4 Hz, 1H), 7.24 (tt, J=7.4, 1.3 Hz, 1H), 6.99 (d, J=9.2 Hz, 2H), 6.86 (d, J=8.4 Hz, 1H), 5.04 (s, 2H), 3.19 (t, 5.0 Hz, 4H), 2.83 (t, J=5.0 Hz, 4H), LRMS: calc. 372.2, found 373.2 (MH) <sup>+</sup> .	J, P, F(with 322), G

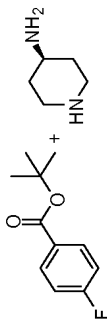
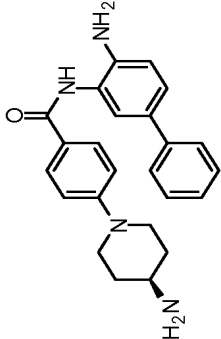
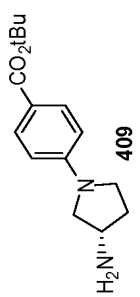
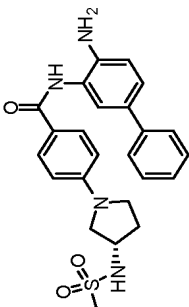
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	477			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-(piperazin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 9.57 (s, 1H), 7.93 (d, J=8.8 Hz, 2H), 7.46 (d, J=2.3 Hz, 1H), 7.36 (dd, J=4.9, 1.0 Hz, 1H), 7.28 (dd, J=8.4, 2.3 Hz, 1H), 7.24 (dd, J=3.5, 1.0 Hz, 1H), 7.06-7.03 (m, 3H), 6.81 (d, J=8.2 Hz, 1H), 5.11 (s, 2H), 3.40 (t, 4.9 Hz, 4H), 3.06 (t, J=5.0 Hz, 4H). LRMS: calc. 378.2, found 379.1 (MH) <sup>+</sup> .	P, N(with 4), W
	478			(R)-methyl 1-((4-(4-amino-4'-fluorobiphenyl-3-yl)-3-ylcarbamoyl)pyrrolidin-3-yl)carbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 10.3 (s, 1H), 8.02 (s, J=8.8 Hz, 2H), 7.84 (d, J=2.0 Hz, 1H), 7.73 (dd, J=9.0, 5.4 Hz, 2H), 7.59 (dd, J=8.4, 2.0 Hz, 1H), 7.56 (bs, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.33 (t, J=8.8 Hz, 2H), 6.61 (d, J=8.8 Hz, 2H), 4.21 (sext, J=5.9 Hz, 1H), 3.57 (m, 1H), 3.55 (s, 3H), 3.46 (m, 1H), 3.36 (m, 1H), 3.18 (dd, J=10.2, 5.0 Hz, 1H), 2.19 (sext, J=6.6 Hz, 1H), 1.94 (sext, J=6.4 Hz, 1H). LRMS: calc. 448.2, found 449.2 (MH) <sup>+</sup> .	K, W

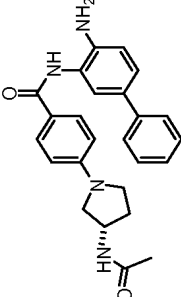
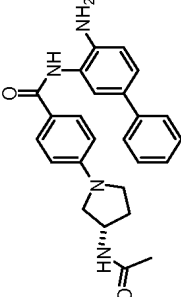
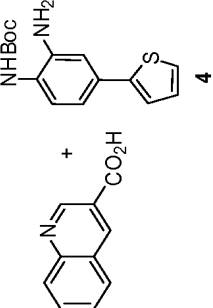
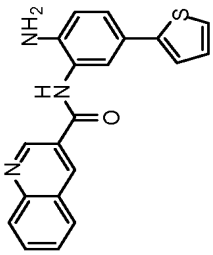
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	479			(S)-N-(4-aminobiphen-1-yl)-4-(3-hydroxypropyl)pyrrolidine-1-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 9.43 (s, 1H), 7.88 (d, J=8.8 Hz, 2H), 7.56 (dd, J=8.4, 1.2 Hz, 2H), 7.51 (d, J=2.0 Hz, 1H), 7.39 (t, J=8.0 Hz, 2H), 7.30 (dd, J=8.2, 2.2 Hz, 1H), 7.24 (tt, J=7.4, 1.3 Hz, 1H), 6.86 (d, J=8.4 Hz, 1H), 6.57 (d, J=9.2 Hz, 2H), 5.02 (d, J=1.2 Hz, 2H), 5.01 (s, 1H), 4.43 (bs, 1H), 3.47 (dd, J=10.6, 4.6 Hz, 1H), 3.36-3.42 (m, 2H), 3.17 (d, J=10.4 Hz, 1H), 2.06 (m, 1H), 1.93 (m, 1H). LRMS: calc. 373.2, found 374.2 (MH) <sup>+</sup> .	J, V, I, F(with 322), O, G
	480			(R)-N-(4-aminobiphen-1-yl)-4-(3-hydroxypropyl)pyrrolidine-1-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 9.44 (s, 1H), 7.88 (d, J=9.2 Hz, 2H), 7.56 (dd, J=8.4, 1.2 Hz, 2H), 7.51 (d, J=2.4 Hz, 1H), 7.39 (t, J=7.8 Hz, 2H), 7.30 (dd, J=8.4, 2.4 Hz, 1H), 7.24 (tt, J=7.3, 1.4 Hz, 1H), 6.86 (d, J=8.4 Hz, 1H), 6.57 (d, J=8.8 Hz, 2H), 5.03 (s, 3H), 4.43 (bs, 1H), 3.47 (dd, J=10.4, 4.8 Hz, 1H), 3.42-3.56 (m, 2H), 3.17 (d, J=10.8 Hz, 1H), 2.06 (m, 1H), 1.93 (m, 1H). LRMS: calc. 373.2, found 374.2 (MH) <sup>+</sup> .	V, I, F(with 322), O, G

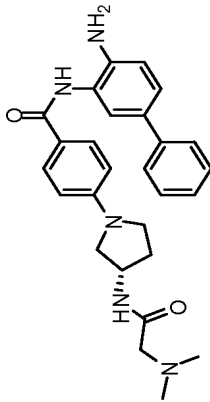
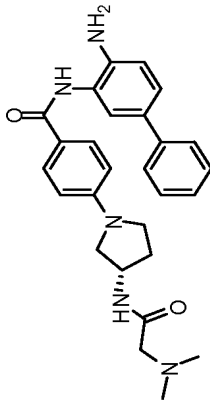
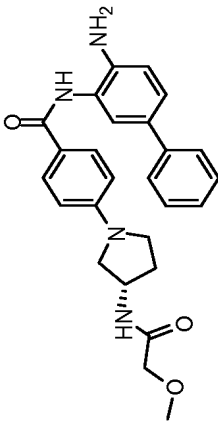
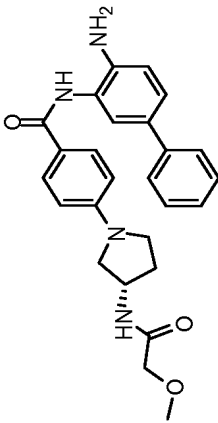


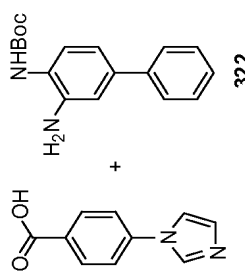
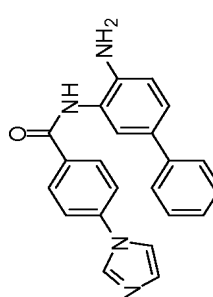
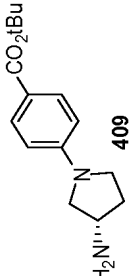
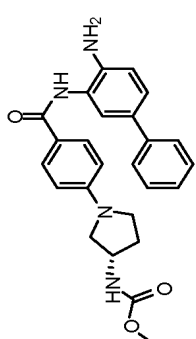
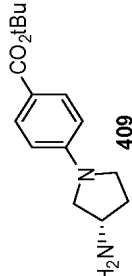
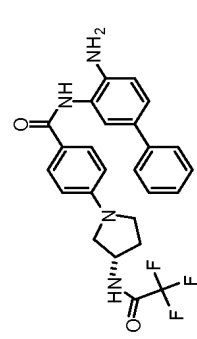
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	481	 <p>409</p>		(S)-4-(3-aminobenzoyl)pyrrolidine-1-yl-4-fluorobiphenyl-3-ylbenzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 9.44 (s, 1H), 8.19 (d, J=6.8 Hz, 1H), 7.89 (d, J=9.2 Hz, 2H), 7.58 (dd, J=8.8, 5.2 Hz, 2H), 7.49 (m, 1H), 7.27 (dd, J=8.4, 2.0 Hz, 1H), 7.21 (t, J=8.8 Hz, 2H), 6.85 (d, J=8.4 Hz, 1H), 6.59 (d, J=9.2 Hz, 2H), 5.02 (m, 2H), 4.38 (m, J=5.3 Hz, 1H), 3.55 (dd, J=10.0, 6.4 Hz, 1H), 3.44 (m, 1H), 3.37 (m, 1H), 3.14 (dd, J=10.0, 4.4 Hz, 1H), 2.19 (sext, J=6.7 Hz, 1H), 1.91 (sext, J=6.1 Hz, 1H), 1.82 (s, 3H). LRMS: calc. 432.2, found 433.3 (MH) <sup>+</sup> .	I, F (with 322), R, V, G
	482	 <p>404</p>		(R)-N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(2-methoxyacetamido)pyrrolidine-1-ylbenzamide	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.43 (s, 1H), 8.10 (d, 1H), 7.88 (d, 2H), 7.59-7.56 (m, 2H), 7.48 (d, 1H), 7.27 (dd, 1H), 7.23 (td, 2H), 6.85 (d, 1H), 6.58 (d, 2H), 5.03 (s, 2H), 4.51-4.46 (m, 1H), 3.82 (s, 2H), 3.59-3.55 (m, 1H), 3.49-3.43 (m, 1H), 3.31-3.34 (m, 1H), 3.30 (s, 3H), 3.24-3.20 (m, 1H), 2.23-2.17 (m, 1H), 2.06-1.97 (m, 1H). LRMS: calc. 462.3, found 463.2 (MH) <sup>+</sup> .	K, G

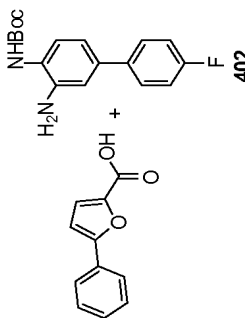
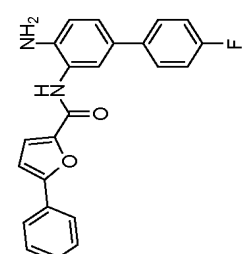
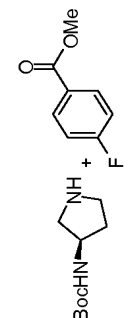
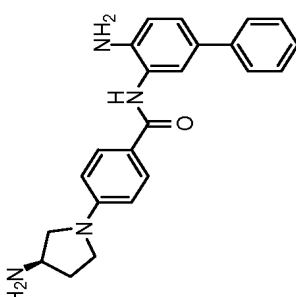
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	483	 404		(R)-N-(4-aminobiphenyl-3-yl)-4-(3-aminopyrrolidin-1-yl)benzamide	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.41(s, 1H), 7.87(d, 2H), 7.59-7.56(m, 2H), 7.48(d, 1H), 7.27(dd, 1H), 7.23(td, 2H), 6.85(d, 1H), 6.55(d, 2H), 5.03(s, 2H), 3.64-3.59(m, 1H), 3.49-3.41(m, 3H), 2.98(dd, 1H), 2.13-2.05(m, 1H), 1.79-1.71(m, 1H). LRMS: calc. 390.2, found 391.3 (MH) <sup>+</sup> .	G
	484	 +		N-(4-aminobiphenyl-3-yl)-4-(3-aminopyrrolidin-1-yl)benzamide	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.53(s, 1H), 8.16(s, 1H), 7.92(dd, 1H), 7.57-7.54(m, 2H), 7.51(d, 1H), 7.39(t, 2H), 7.31(dd, 1H), 7.23(tt, 1H), 6.98(d, 2H), 6.86(d, 1H), 5.05(s, 2H), 3.85(s, 2H), 3.54(t, 2H). LRMS(ESI): (calc.) 386.2 (found) 387.2 (MH) <sup>+</sup> .	J, I, F(with 322), G

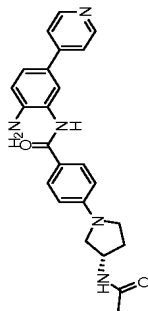
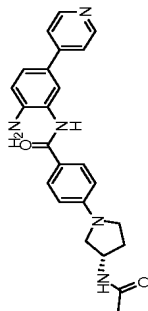
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	485			N-(4-aminobiphen-3-yl)-4-(4-aminopiperidin-1-yl)benzamide	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.48 (s, 1H), 7.87 (d, J= 9.1 Hz, 2H), 7.55 (dd, J= 1.3, 8.3 Hz, 2H), 7.50 (d, J= 2.1 Hz, 1H), 7.39 (dt, J= 2.1, 7.4 Hz, 2H), 7.30 (dd, J= 2.1, 8.3 Hz, 1H), 7.24 (dt, J= 1.3, 7.4 Hz, 1H), 6.99 (d, J= 9.1 Hz, 2H), 6.86 (d, J= 8.3 Hz, 1H), 5.04 (bs, 2H), 3.82 (d, J= 12.7 Hz, 2H), 2.86 (dt, J= 2.5, 12.0 Hz, 2H), 2.81 – 2.75 (m, 1H), 1.76 (dd, J= 3.3, 12.5 Hz, 2H), 1.32 – 1.22 (m, 2H). Alkyl NH <sub>2</sub> overlapped LRMS(ESI): (calc.) 386.2 (found) 387.2 (MH) <sup>+</sup>	J, T, I, F(with 322), R, G
	486			(S)-N-(4-aminobiphen-3-yl)-4-(3-(methylsulfonyl)pyrrolidin-1-yl)benzamide	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.45 (s, 1H), 7.89 (d, J= 8.8 Hz, 2H), 7.57 to 7.51 (m, 3H), 7.48 (d, J= 6.4 Hz, 1H), 7.39 (dt, J= 6.4, 1.9 Hz, 2H), 7.30 (dd, J= 8.4, 2.3 Hz, 1H), 7.24 (dt, J= 7.4, 1.2 Hz, 1H), 6.86 (d, J= 8.2 Hz, 1H), 6.60 (d, J= 8.8 Hz, 2H), 5.01 (bs, 2H), 4.08 (dd, J= 6.3, 12.5 Hz, 1H), 3.63 (dd, J= 6.6, 10.0 Hz, 1H), 3.48 – 3.43 (m, 1H), 3.33 (s, 3H), 3.20 (dd, J= 5.5, 10.2 Hz, 1H), 2.3 – 2.25 (m, 1H), 2.00 – 1.96 (m, 1H) (one overlapped H). LRMS(ESI): (calc.) 450.17 (found) 451.2 (MH) <sup>+</sup>	U, I, F(with 322), G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	487	 409		(S)-4-(3-aminobenzamido)pyrrolidin-1-yl-N-(4-aminobiphenyl-3-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.42 (s, 1H), 8.20 (d, 1H), 7.88 (d, 2H), 7.55 (d, 2H), 7.50 (s, 1H), 7.40 (t, 2H), 7.31 (dd, 1H), 7.22 (t, 1H), 6.84 (d, 1H), 6.59 (d, 2H), 5.01 (s, 2H), 4.39 (m, 1H), 3.52 (m, 1H), 3.42 (m, 1H), 3.38 (m, 1H), 3.11 (dd, 1H), 2.21 (m, 1H), 1.90 (m, 1H), 1.80 (s, 3H). LRMS: (calc.) 414.50 (found) 415.3 (MH) <sup>+</sup>	V, I, F(with 322), G
	488	 4		N-(2-amino-5-(thiophen-2-yl)phenyl)quinoline-3-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 10.83 (0.3H, s), 9.55 (1H, d, J=1.9 Hz), 9.27 (1H, s), 8.23 (1H, d, J=8.0 Hz), 8.19 (1H, d, J=8.5 Hz), 8.02-7.97 (1H, m), 7.83-7.79 (1H, m), 7.76 (1H, s), 7.61 (1H, d, J=2 Hz), 7.58 (1H, d, J=2 Hz), 7.53 (1H, d, J=4.9 Hz), 7.47 (1H, d, J=3.5 Hz), LRMS: 345.09 (calc) 346.0 (found)	F, W

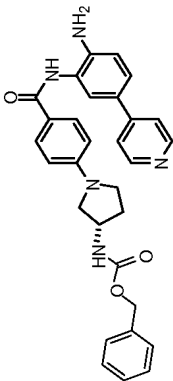
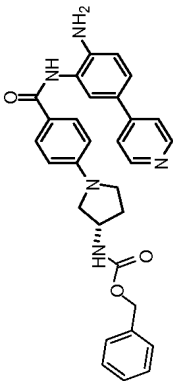
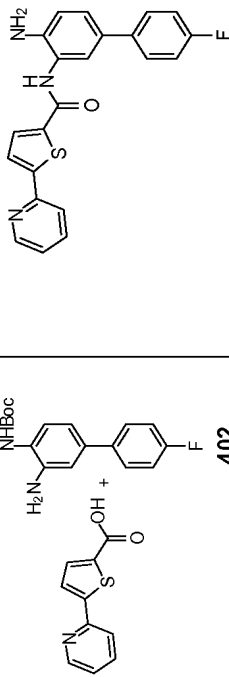
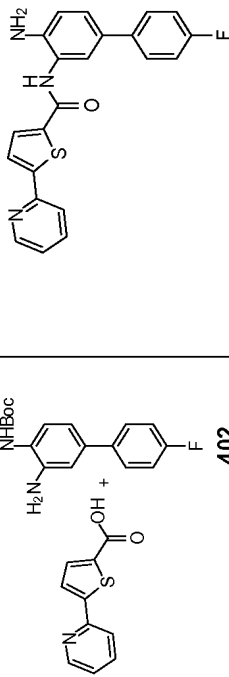
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	489			(S)-N-(4-aminobiphen-1-yl)-4-(3-(2-(dimethylamino)acetamido)pyrrolidin-1-yl)benzamide	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.43(s, 1H), 8.00(d, 2H), 7.88(d, 2H), 7.54(dd, 2H), 7.49(d, 1H), 7.38(t, 2H), 7.28(d, 1H), 7.24-7.20(m, 1H), 6.85(d, 1H), 6.57(d, 2H), 5.02(s, 2H), 4.46-4.42(m, 1H), 3.57-3.52(m, 1H), 3.44-3.40(m, 1H), 3.34(s, 3H), 3.20-3.16(m, 1H), 2.86(s, 2H), 2.20-2.00(m, 7H), 1.99-1.96(m, 1H), LRMS(ESI): (calc.) 457.57 (found) 458.3 (MH) <sup>+</sup>	T, I, F(with 322), R, F, G
	490			(S)-N-(4-aminobiphen-1-yl)-4-(3-(2-methoxyacetamido)pyrrolidin-1-yl)benzamide	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.43(s, 1H), 8.09(d, 2H), 7.87(d, 2H), 7.54(dd, 2H), 7.49(d, 1H), 7.38(m, 2H), 7.28(d, 1H), 7.24-7.20(m, 1H), 6.84(d, 1H), 6.57(d, 2H), 5.01(s, 2H), 4.49-4.44(m, 1H), 3.81(s, 2H), 3.57-3.52(m, 1H), 3.45(m, 1H), 3.34(s, 3H), 3.18(m, 1H), 2.16(m, 1H), 2.04(m, 1H), LRMS(ESI): (calc.) 444.53 (found) 445.2(MH) <sup>+</sup>	T, I, F(with 322), R, K, G

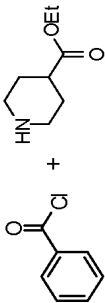
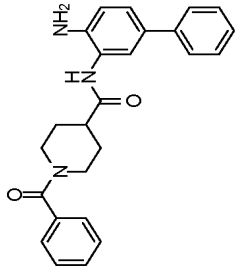
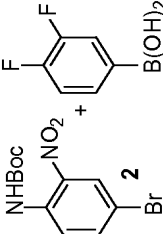
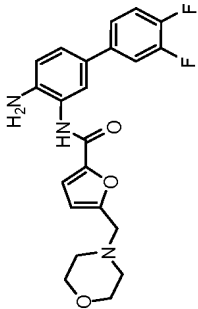
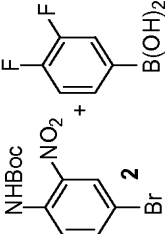
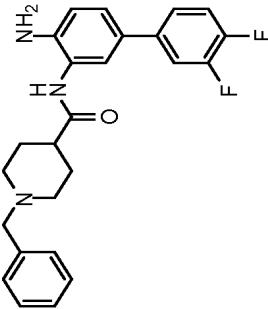
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	491			(S)-N-(4-aminobiphenyl-3-yl)-4-(3-methoxyacetamidopyrrolidin-1-yl)benzamide	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.81(s, 1H), 8.42(s, 1H), 8.14(d, 2H), 7.85(s, 1H), 7.82(d, 2H), 7.56-7.51(m, 3H), 7.40-7.32(m, 3H), 7.22(m, 1H), 7.15(s, 1H), 6.84(d, 1H), 6.86(d, 2H), 5.13(s, 2H).LRMS(ESI): (calc.) 444.53 (found) 445.2(MH) <sup>+</sup>	F, G
	492			(S)-N-(4-aminobiphenyl-3-yl)-4-(3-methoxyacetamidopyrrolidin-1-yl)benzamide	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.42(s, 1H), 7.87(d, 2H), 7.55-7.49(m, 3H), 7.39(t, 2H), 7.32(dd, 1H), 7.27-7.20(m, 1H), 6.84(d, 1H), 6.56(d, 2H), 5.01(s, 2H), 4.19(m, 1H), 3.50-3.52(m, 4H), 3.42(m, 1H), 3.15(m, 1H), 2.18(m, 1H), 1.93(m, 1H). LRMS(ESI): (calc.) 444.53 (found) 445.2 (MH) <sup>+</sup>	K, I, F(with 322), G
	493			(S)-N-(4-aminobiphenyl-3-yl)-4-(3-methoxyacetamidopyrrolidin-1-yl)benzamide	<sup>1</sup> HNMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.82(d, 1H), 9.53(s, 1H), 7.97(d, 2H), 7.63-7.58(m, 3H), 7.47(t, 2H), 7.37(dd, 1H), 7.22(t, 1H), 7.31(dt, 1H), 6.93(d, 1H), 6.68(d, 2H), 5.10(s, 2H), 4.60(m, 1H), 3.70(m, 1H), 3.56(m, 1H), 3.44(m, 1H), 2.35(m, 1H), 2.15(m, 1H). RMS: (calc.) 468.47 (found) 469.1 (MH) <sup>+</sup>	K, I, F(with 322), G

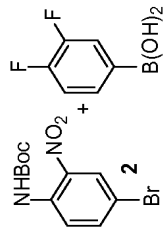
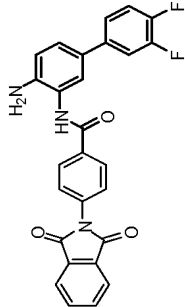
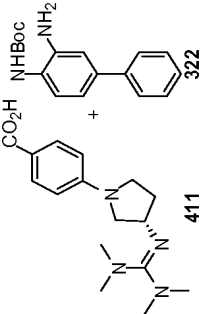
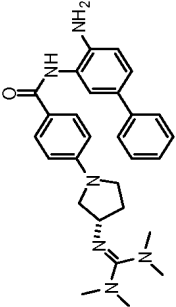
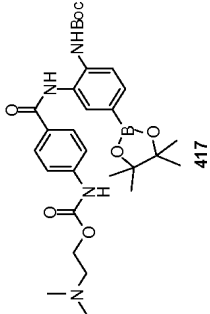
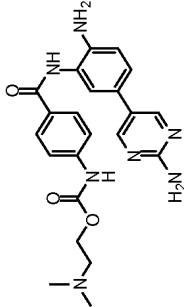
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	494			N-(4-amino-2-phenylfuran-3-yl)-5-fluorobiphenyl-3-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 9.86 (br s, 1H), 8.02 (d, J = 7.2 Hz, 1H), 7.68-7.60 (m, 2H), 7.58-7.50 (m, 3H), 7.47-7.36 (m, 3H), 7.30-7.20 (m, 3H), 6.92 (d, J = 8.4 Hz, 1H), 5.18 (br s, 2H). LRMS(ESI): (calc.) 372.4 (found) 373.3 (MH)+	F, G
	495			(R)-N-(4-aminobiphenyl-3-yl)-4-(3-aminopyrrolidin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 9.45 (s, 1H), 7.88 (d, J=8.6 Hz, 2H), 7.54 (dd, J=7.2, 1.2 Hz, 2H), 7.50 (d, J= 2.4 Hz, 1H), 7.37 (t, J=7.4 Hz, 2H), 7.28 (dd, J=8.2, 2.2 Hz 1H), 7.22 (tt, J=7.4, 1.2 Hz, 1H), 6.85 (d, J=8.2 Hz, 1H), 6.57 (d, J=8.8 Hz, 2H), 5.00(d, J=10.2 Hz, 1H) 3.76 (quint, J=4.5 Hz, 1H), 3.54-3.40 (m, 3H), 3.15 (dd, J=10.4, 4.1 Hz, 1H), 2.19 (sext, J=6.3 Hz, 1H), 1.91 (sext, J=5.1 Hz, 1H). LRMS: (calc.) 372.5 (found) 373.2 (MH)+	J, P, F(with 322), G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	496	 409		(S)-4-(3-acetamidopyrrolidin-1-yl)-N-(2-amino-5-(pyridin-4-yl)phenyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 1H:9.43 (s, 1H), 8.49 (d, J=6.3 Hz, 2H), 8.18 (d, J=6.8 Hz, 1H), 7.88 (d, J=9.0 Hz, 2H), 7.66 (d, J=2.2 Hz, 1H), 7.57 (d, J=6.3 Hz, 2H), 7.47 (dd, J=8.6, 2.2 Hz, 1H), 6.87 (d, J=8.4 Hz, 1H), 6.58 (d, J=9.0 Hz, 2H), 5.29 (s, 2H), 4.38 (quint, J=5.1 Hz, 1H), 3.54 (dd, J=9.8, 6.5 Hz, 1H), 3.47-3.42 (m, 1H), 3.37-3.32 (m, 1H), 3.12 (dd, J=10.2, 4.1 Hz, 1H), 2.17 (sext, J=5.1 Hz, 1H), 1.90-1.87 (m, 1H), 1.81 (s, 3H). LRMS: (calc.) 415.5 (found) 416.2 (MH) <sup>+</sup>	V, I, F(with 390), G

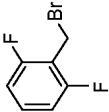
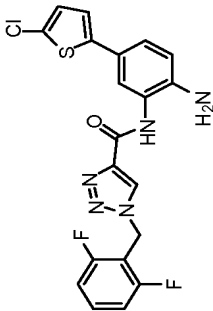
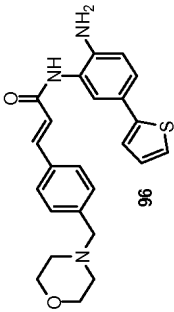
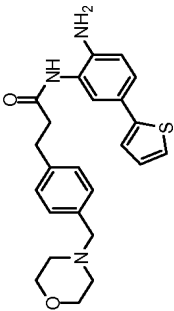
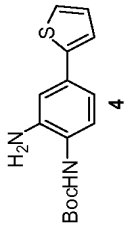
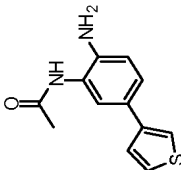


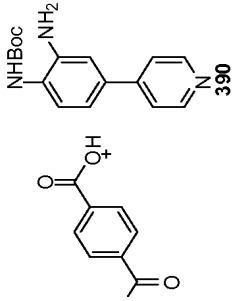
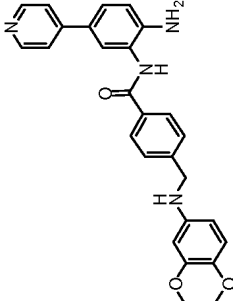
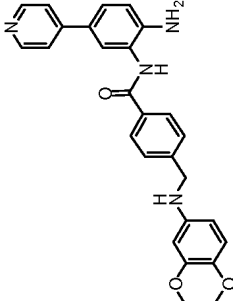
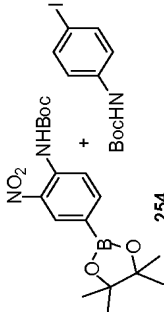
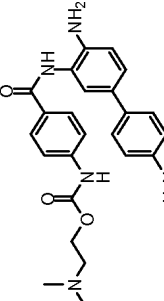
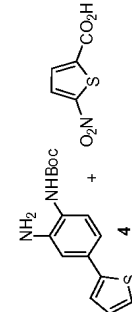
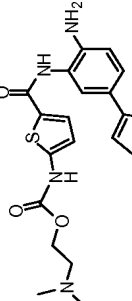
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	497	 409	 409	(S)-benzyl 1-(4-(2-amino-5-(pyridin-4-yl)phenyl)carbamoyl)phenylpyrrolidin-3-ylcarbamate	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 8.43 (d, J=6.5 Hz, 2H), 7.88 (d, J=8.8 Hz, 2H), 7.62 (d, J=2.2 Hz, 1H), 7.60 (d, J=6.5 Hz, 2H), 7.48 (dd, J=8.4, 2.3 Hz, 1H), 7.34-7.27 (m, 5H), 6.96 (d, J=8.4 Hz, 1H), 6.57 (d, J=8.8 Hz, 2H), 5.48 (s, 2H), 5.08 (s, 2H), 4.30 (quint, J=5.1 Hz, 1H), 3.59 (dd, J=10.2, 6.7 Hz, 1H), 3.46 (dt, J=9.0, 7.4 Hz, 1H), 3.35 (q, J=7.4 Hz, 1H), 3.21 (dd, J=9.8, 4.9 Hz, 1H), 2.26 (sext, J=7.2 Hz, 1H), 1.99 (sext, J=6.8 Hz, 1H). LRMS: (calc.) 507.6 (found) 508.3 (MH) <sup>+</sup>	T, I, F(with 390), G
	498	 402	 402	N-(4-amino-4'-fluorobiphenyl-5-yl-3-yl)-5-(pyridin-2-yl)thiophene-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.60-8.55 (m, 1H), 7.98-7.86 (m, 3H), 7.78 (d, J = 3.9 Hz, 1H), 7.63-7.56 (m, 2H), 7.48 (d, J = 2.2 Hz, 1H), 7.40-7.34 (m, 2H), 7.19-7.11 (m, 2H), 7.00 (d, J = 8.4 Hz, 1H). LRMS(ESI): (calc.) 389.5 (found) 390.2 (MH) <sup>+</sup>	F, G

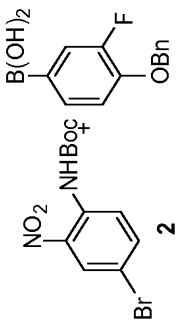
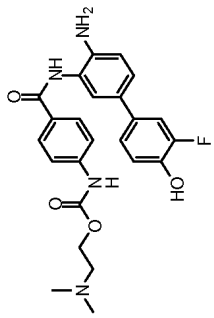
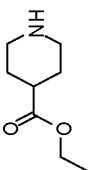
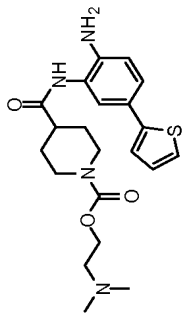
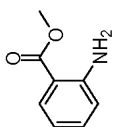
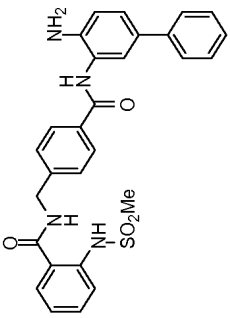
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	<b>499</b>			N-(4-aminobiphenyl-3-yl)-1-benzoylpiperidine-4-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.25 (s, 1H), 7.60-7.53 (m, 3H), 7.52-7.46 (m, 3H), 7.46-7.40 (m, 4H), 7.32-7.24 (m, 2H), 6.84 (d, J = 8.2 Hz, 1H), 4.66-4.45 (br m, 1H), 3.80-3.62 (br m, 1H), 3.22-2.84 (br m, 2H), 2.80-2.70 (m, 1H), 2.06-1.80 (br m, 2H), 1.76-1.58 (br m, 2H). LRMS(ESI): (calc.) 399.5 (found) 400.4 (MH)+	K, P, F(with 322), G
	<b>500</b>			N-(4-amino-3',4'-difluorobiphenyl-3-yl)-5-(morpholino(methyl)furan-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.46-8.44 (m, 2H), 7.72 (d, J=2.2 Hz, 1H), 7.62-7.60 (m, 2H), 7.46 (dd, J=8.4, 2.3 Hz, 1H), 7.13-7.03 (m, 4H), 6.94 (d, J=8.4 Hz, 1H), 3.84 (s, 2H), 3.43 (s, 2H), 2.98-2.92 (m, 4H). LRMS: (calc.) 413.4 (found) 414.3 (MH)+.	B, C, F, G
	<b>501</b>			N-(4-amino-3',4'-difluorobiphenyl-3-yl)-1-benzoylpiperidine-4-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 7.50-7.23 (m, 10H), 6.96-6.90 (m, 1H), 3.59 (s, 2H), 3.09-3.00 (m, 2H), 2.56-2.44 (m, 1H), 2.20-2.10 (m, 2H), 2.00-1.89 (m, 4H). LRMS: (calc.) 421.5 (found) 422.3 (MH)+	B, C, F, G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	502	 2		N-(4-amino-3',4'-difluorobiphenyl-3-yl)-4-(1,3-dioxoisindol-2-yl)benzamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 9.86 (s, 1H), 8.22-8.14 (m, 2H), 8.08-7.94 (m, 4H), 7.71-7.60 (m, 4H), 7.52-7.37 (m, 3H), 6.94-6.86 (m, 1H), 5.30 (s, 2H). LRMS: (calc.) 469.4 (found) 470.3 (MH) <sup>+</sup>	B, C, F, G
	503	 411 + 322		(S)-N-(4-aminobiphenyl-3-yl)-4-(3-(bis(dimethylamino)methyl)eneamino)pyrrolidin-1-yl)benzamide	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.46 (s, 1H), 7.88 (d, 2H), 7.55-7.49 (m, 3H), 7.39 (t, 2H), 7.29 (dd, 1H), 7.22 (t, 1H), 6.85 (d, 1H), 6.60 (d, 2H), 5.02 (s, 2H), 4.18 (m, 1H), 3.61 (m, 1H), 3.50 (s, 3H), 3.21 (m, 1H), 2.85-2.78 (m, 9H), 2.27 (m, 2H), 1.97 (m, 2H). LRMS: (calc.) 470.72 (found) 471.4 (MH) <sup>+</sup>	F, G
	504	 417		2-(dimethylamino)ethyl 4-(2-amino-5-(2-aminopyrimidin-5-yl)phenyl)carbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.01 (s, 1H), 9.64 (s, 1H), 8.44 (s, 2H), 7.94 (d, J=8.8 Hz, 2H), 7.59 (d, J=8.8 Hz, 2H), 7.40 (d, J=2.0 Hz, 1H), 7.24 (dd, J1=8.4 Hz, J2=2.0 Hz, 1H), 6.84 (d, J=8.4 Hz, 1H), 6.59 (s, 2H), 5.01 (s, 2H), 4.19 (t, J=6.0 Hz, 2H), 2.52 (t, J=5.6 Hz, 2H, overlapped DMSO-d <sub>6</sub> ), 2.19 (s, 6H). LRMS: (calc.) 435.38 (found) 436.2 (MH) <sup>+</sup>	B, G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	<b>505</b>			2-(dimethylamino)ethyl 4-(4-amino-3',4',5'-trimethoxybiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.02 (s, 1H), 9.67 (s, 1H), 7.95 (d, J=8.8 Hz, 2H), 7.59 (d, J=8.8 Hz, 2H), 7.46 (d, J=1.6 Hz, 1H), 7.34 (dd, J1=8.4 Hz, J2=2.4 Hz, 1H), 6.85 (d, J=8.4 Hz, 1H), 6.79 (s, 2H), 5.02 (s, 2H), 4.19 (t, J=5.6 Hz, 2H), 3.83 (s, 6H), 3.66 (s, 3H), 2.52 (t, J=5.6 Hz, 2H, overlapped (DMSO-d <sub>6</sub> ), 2.19 (s, 6H). LRMS: (calc.) 508.57 (found) 509.2 (MH) <sup>+</sup>	B, G
	<b>506</b>			N-(2-amino-5-(pyridin-3-yl)phenyl)-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.81 (s, 1H), 8.75 (d, J = 2 Hz, 1H), 8.73 (s, 1H), 8.41 (dd, J = 1.6 Hz, 4.4 Hz, 1H), 7.91 (m, 1H), 7.58 (d, J = 2 Hz, 1H), 7.52 (m, 1H), 7.38 (m, 2H), 7.20 (t, J = 8 Hz, 2H), 6.86 (d, J = 8 Hz, 1H), 5.76 (s, 2H), 5.17 (s, 2H). LRMS: (calc.) 406.2 (found) 407.3 (MH) <sup>+</sup>	Y, P, F, W
	<b>507</b>			N-(2-amino-5-(thiophen-2-yl)phenyl)-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.61 (s, 1H), 7.77 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.43-7.54 (m, 4H), 7.08-7.13 (m, 3H), 5.82 (s, 2H). LRMS: (calc.) 411.1 (found) 412.3 (MH) <sup>+</sup>	Y, P, F(with 4), W

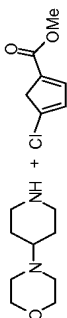
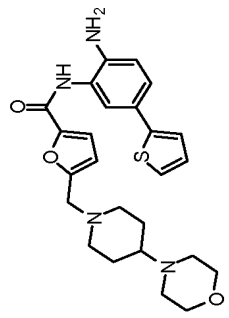
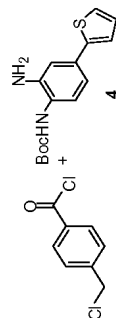
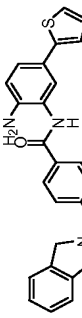
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	508			N-(2-amino-5-(5-chlorothiophen-2-yl)phenyl)-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) □ (ppm): 7.52 (m, 2H), 7.26 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 7.09 (t, J = 8 Hz, 2H), 7.01 (d, J = 4 Hz, 1H), 6.88 (dd, J = 2.4 Hz, 6.4 Hz, 2H), 5.80 (s, 2H). LRMS: (calc.) 445.8 (found) 446.3 (MH) <sup>+</sup>	Y, P, F(with 168), W
	509			N-(2-amino-5-(thiophen-2-yl)phenyl)-3-(4-(morpholino)methyl)phenylpropanamide	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.17(s, 1H), 7.42 (d, 1H), 7.34 (dd, 1H), 7.22-7.17 (m, 6H), 7.04 (dd, 1H), 6.72 (d, 1H), 5.02 (s, 2H), 3.54 (t, 4H), 3.41 (s, 2H), 2.90 (t, 2H), 2.63 (t, 2H), 2.32-2.27 (m, 4H). LRMS: (calc.) 421.3 (found) 422.2 (MH) <sup>+</sup>	C
	510			N-(2-amino-5-(thiophen-3-yl)phenyl)acetamide	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.20 (s, 1H), 7.55 (dd, 1H), 7.52 (dd, 1H), 7.48 (d, 1H), 7.37 (dd, 1H), 7.26 (dd, 1H), 6.73 (dd, 1H), 5.21 (s, 2H), 2.04 (s, 3H). LRMS: 232.1 (calc) 233.0 (found for M+H)	V, G

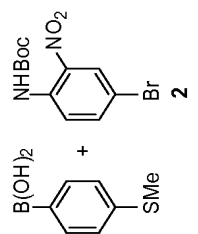
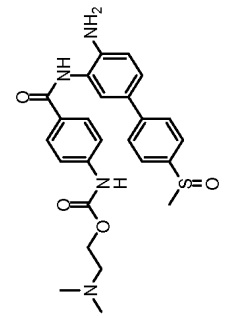
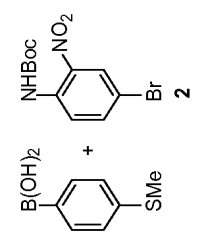
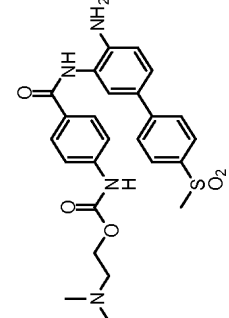
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	511	  390		N-(2-amino-5-(pyridin-4-yl)phenyl)-4-((3,4-dimethoxyphenylamino)methyl)benzamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.50 - 8.38 (m, 2H), 7.96 (d, J=8.2 Hz, 2H), 7.66 - 7.64 (m, 3H), 7.55 - 7.51 (m, 3H), 6.98 (d, J=8.4 Hz, 1H), 6.71 (d, J=8.6 Hz, 1H), 6.36 (d, J=2.5 Hz, 1H), 6.13 (dd, J=8.6, 2.5 Hz, 4.37 (s, 2H), 3.73 (s, 3H), 3.70 (s, 3H). LRMS: (calc.) 454.2 (found) 455.3 (MH) <sup>+</sup>	F, Z, G
	512	 254		2-(dimethylamino)ethyl 4-(4,4'-diaminobiphenyl-3-yl)carbamoyl phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.02 (s, 1H), 9.62 (s, 1H), 7.93 (d, J=8.8 Hz, 2H), 7.58 (d, J=8.8 Hz, 2H), 7.34 (d, J=2.2 Hz, 1H), 7.21 (d, J=6.6 Hz, 2H), 7.15 (d, J=8.4 Hz, 1H), 6.78 (d, J=8.3 Hz, 1H), 6.58 (d, J=8.4 Hz, 2H), 5.02 (s, 2H), 4.82 (s, 2H), 4.17 (t, J=5.6 Hz, 2H), 2.53 (t, J=5.5 Hz, 2H), 2.18 (s, 6H). LRMS(ESI): (calc.) 433.13 (found) 434.3 (MH) <sup>+</sup>	B, C, F, G
	513	 4		2-(dimethylamino)ethyl 5-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)thiophenylcarbamate	<sup>1</sup> H NMR: (CD <sub>3</sub> OD) δ (ppm): 7.66 (d, 1H), 7.45 (d, 1H), 7.33 (dd, 1H), 7.20 (m, 2H), 7.00 (dd, 1H), 6.88 (d, 1H), 6.61 (d, 1H), 4.31 (t, 2H), 2.68 (t, 2H), 2.32 (s, 6H). LRMS: (calc.) 430.66 (found) 431.1 (MH) <sup>+</sup>	F, C, AA, G

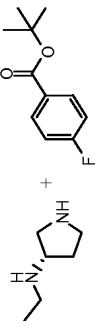
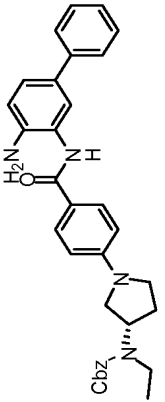
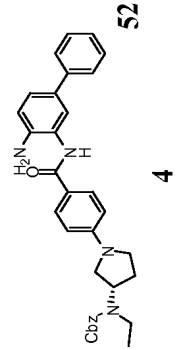
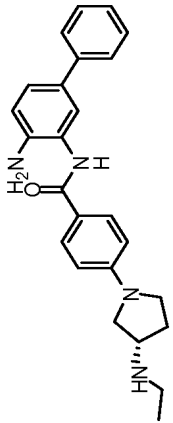
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	<b>514</b>	 <chem>BrC1=CC=C(C(=C1)C(=O)O)C(=O)O</chem> <b>2</b>		2-(dimethylamino)ethyl 4-(4-amino-3'-fluoro-4'-hydroxybiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 10.01 (s, 1H), 9.77 (s, 1H), 9.61 (s, 1H), 7.94 (d, 2H), 7.59-7.57 (m, 2H), 7.41 (d, 1H), 7.29 (dd, 1H), 7.23 (dd, 1H), 7.17 (dd, 1H), 6.94 (t, 1H), 6.81 (d, 1H), 5.01 (s, 2H), 4.18 (t, 2H), 2.52 (t, 2H), 2.18 (s, 6H). LRMS: (calc.) 452.59 (found) 453.2 (MH) <sup>+</sup>	B, C, F (with <b>335</b> ), G
	<b>515</b>			2-(dimethylamino)ethyl 4-(2-amino-5-(thiophen-2-yl)phenylcarbamoyl)piperidine-1-carboxylate	<sup>1</sup> H NMR: (DMSO-d <sub>6</sub> ) δ (ppm): 9.23 (s, 1H), 7.50 (d, 1H), 7.32 (dd, 1H), 7.21-7.17 (m, 2H), 7.01 (dd, 1H), 6.72 (d, 1H), 5.09 (s, 2H), 4.07 (t, 2H), 4.01 (m, 2H), 2.81 (s, 2H), 2.48 (t, 2H), 2.18 (s, 6H), 1.82 (m, 2H), 1.53 (m, 2H). LRMS: (calc.) 416.54 (found) 417.2 (MH) <sup>+</sup>	BB, E, CC, K (with <b>4</b> ), G
	<b>516</b>			N-(4-(4-aminobiphenyl-3-ylcarbamoyl)benzyl)-2-(methylsulfonamido)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 11.13 (s, 1H), 10.27 (s, 1H), 9.58 (t, J = 6.0 Hz, 1H), 8.05 (d, J = 8.2 Hz, 2H), 7.94 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 1.8 Hz, 1H), 7.65-7.63 (m, 2H), 7.60-7.50 (m, 5H), 7.46 (t, J = 7.7 Hz, 2H), 7.34 (t, J = 7.3 Hz, 1H), 7.28-7.21 (m, 2H), 4.58 (d, J = 5.9 Hz, 2H), 3.12 (s, 3H). LRMS: Cal.: 514.2; Obt: 515.2 (M+H) <sup>+</sup>	U, P, N, P, CC, K (with <b>322</b> ), W

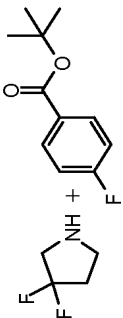
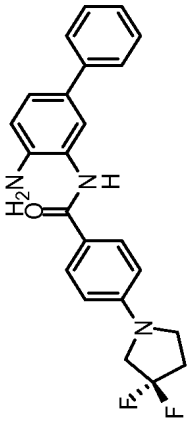
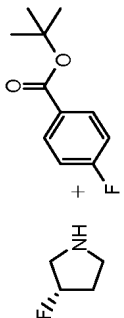
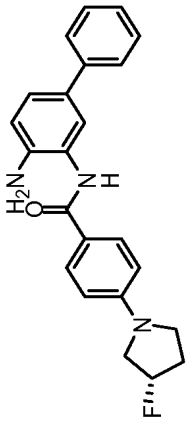


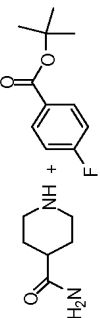
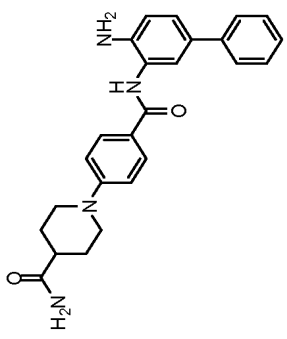
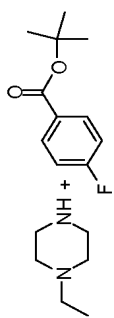
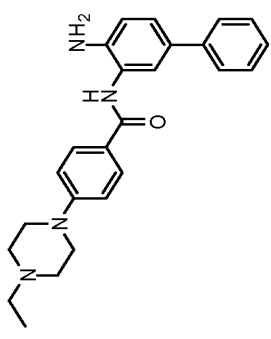


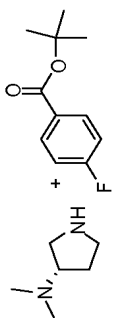
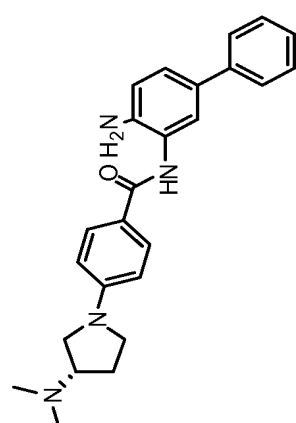
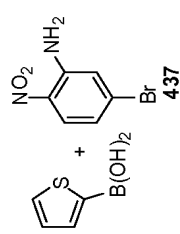
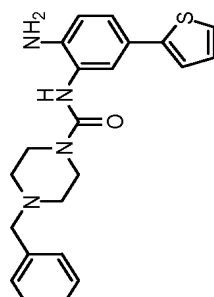
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	<b>520</b>			N-(2-amino-5-((4-morpholin-1-yl)methyl)phenyl)-2-yl)phenyl)-4-(isoindolin-2-ylmethyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.59 (s, 1H), 7.42 (d, J=2.4 Hz, 1H), 7.35 (dd, J1=5.2 Hz, J2=1.2 Hz, 1H), 7.29 (dd, J1=8.4 Hz, J2=2.4 Hz, 1H), 7.24 (dd, J1=3.6 Hz, J2=1.2 Hz, 1H), 7.05 (dd, J1=5.2 Hz, J2=4.0 Hz, 1H), 6.80 (d, J=8.4 Hz, 1H), 6.48 (d, J=3.2 Hz, 1H), 5.14 (s, 2H), 3.54 (s, 6H), 2.88 (d, J=11.6 Hz, 2H), 2.43 (t, J=4.4 Hz, 4H), 2.08 (tt, J1=11.2 Hz, J2=3.6 Hz, 1H), 1.99 (t, J=10.8 Hz, 2H), 1.74 (d, J=11.6 Hz, 2H), 1.38 (qd, J1=12.0 Hz, J2=3.6 Hz, 2H). LRMS: 466.6 (calc) 467.1 (found)	D, E, N (with <b>4</b> ), G
	<b>521</b>			N-(2-amino-5-((4-morpholin-1-yl)methyl)phenyl)-2-yl)phenyl)-4-(isoindolin-2-ylmethyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.71 (s, 1H), 7.98 (d, J=8.4 Hz, 2H), 7.51 (d, J=8.4 Hz, 2H), 7.46 (d, J=1.8 Hz, 1H), 7.34 (dd, J=5.1, 1.2 Hz, 1H), 7.28 (dd, J=8.4, 2.2 Hz, 1H), 7.23 (dd, J=3.5, 1.2 Hz, 1H), 7.23-7.16 (m, 4H), 7.03 (dd, J=5.1, 3.5 Hz, 1H), 6.80 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 3.94 (s, 2H), 3.85 (s, 4H). LRMS: 425.55 (calc) 426.1 (found)	K, L, G

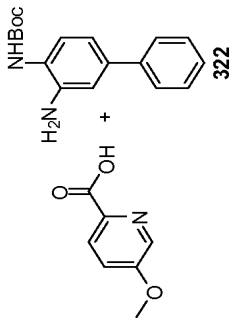
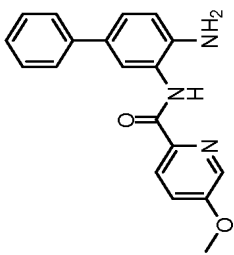
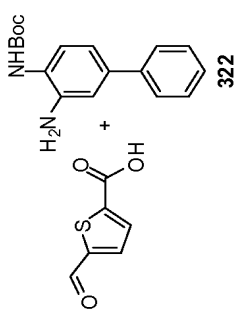
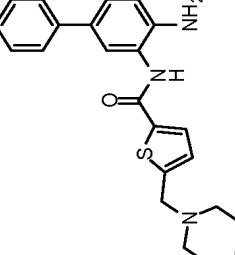
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	522			2-(dimethylamino)ethyl 4-(4-amino-4'-(methylsulfonyl)biphenyl-3-yl)carbamoylphenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 10.04 (s, 1H), 9.63 (s, 1H), 8.58 (s, J=2.0 Hz, 1H), 7.97 (d, J=8.8 Hz, 2H), 7.76-7.67 (m, 2H), 7.61-7.59 (m, 3H), 7.41-7.37 (m, 2H), 6.88 (d, J=8.4 Hz, 1H), 5.23 (s, 2H), 4.22 (t, J=5.6 Hz, 2H), 2.75 (s, 3H), 2.61 (bs, 2H), 2.26 (s, 6H).. LRMS: (calc.) 480.58 (found) 481.4 (MH) <sup>+</sup>	B, C, F (with 335), G, EE
	523			2-(dimethylamino)ethyl 4-(4-amino-4'-(methylsulfonyl)biphenyl-3-yl)carbamoylphenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) □ (ppm): 10.18 (s, 1H), 9.67 (s, 1H), 7.98 (d, J=8.8 Hz, 2H), 7.77-7.68 (m, 4H), 7.62-7.58 (m, 3H), 7.40 (dd, J1=8.4 Hz, J2=2.4 Hz, 1H), 6.88 (d, J=8.4 Hz, 1H), 5.76 (s, 1H), 5.21 (s, 1H), 4.61 (t, J=5.6 Hz, 2H), 3.67 (bs, overlapped water, 2H), 3.23 (s, overlapped water, 6H), 2.75 (s, 3H) LRMS: (calc.) 496.58 (found) 497.2 (MH) <sup>+</sup>	B, C, F (with 335), G, EE

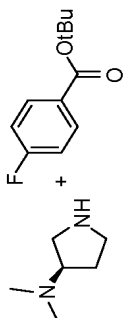
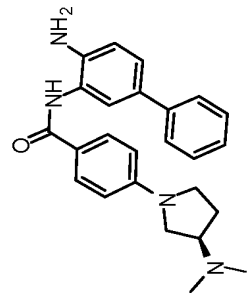
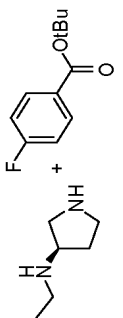
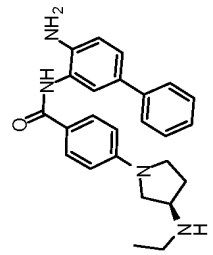
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	524			(S)-benzyl 1-(4-(4-aminobiphenyl-3-ylcarbamoyl)pyrrolidin-3-yl(ethyl)carbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.43 (s, 1H), 7.88 (d, J=9.0 Hz, 2H), 7.54 (d, J=7.0 Hz, 2H), 7.49 (d, J=2.2 Hz, 1H), 7.39-7.31 (m, 6H), 7.29 (dd, J=8.2, 2.2 Hz, 1H), 7.22 (t, J=7.2 Hz, 1H), 6.85 (d, J=8.2 Hz, 1H), 6.60 (d, J=8.8 Hz, 2H), 5.11 (s, 1H), 5.02 (s, 2H), 4.66 (quint, J=8.2 Hz, 1H), 3.51 (t, J=9.8 Hz, 1H), 3.51-3.45 (m, 2H), 3.30-3.24 (m, 4H), 2.21-2.16 (m, 2H), 1.09 (t, J=7.0 Hz, 3H). LRMS(ESI): (calc.) 534.6 (found) 535.3 (MH) <sup>+</sup>	J, T, I, CC, K(with 322), G
	525			(S)-N-(4-aminobiphenyl-3-yl)-4-(3-(ethylamino)pyrrolidin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.41 (s, 1H), 7.87 (d, J=9.0 Hz, 2H), 7.54 (d, J=7.2 Hz, 2H), 7.49 (d, J=2.2 Hz, 1H), 7.38 (t, J=7.2 Hz, 2H), 7.28 (dd, J=8.4, 2.3 Hz, 1H), 7.22 (t, J=7.4 Hz, 1H), 6.85 (d, J=8.4 Hz, 1H), 6.56 (d, J=9.0 Hz, 2H), 5.01 (s, 2H), 3.49 (dd, J=10.0, 6.3 Hz, 1H), 3.41-3.38 (m, 2H), 3.32-3.26 (m, 1H), 3.08 (dd, J=10.0, 6.3 Hz, 1H), 2.78-2.73 (m, 2H), 2.13 (sext, J=7.3 Hz, 1H), 1.83 (sext, J=6.8 Hz, 1H), 1.03 (t, J=7.0 Hz, 3H). LRMS(ESI): (calc.) 400.52 (found) 401.2 (MH) <sup>+</sup>	R

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	526			N-(4-aminobiphen-3-yl)-4-(3,3-difluoropyrrolidin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.49 (s, 1H), 7.91 (d, J=9.0 Hz, 2H), 7.54 (d, J=7.2 Hz, 2H), 7.49 (d, J=2.0 Hz, 1H), 7.37 (t, J=7.4 Hz, 2H), 7.29 (dd, J=8.2, 2.2 Hz, 1H), 7.22 (t, J=7.4 Hz, 1H), 6.85 (d, J=8.2 Hz, 2H), 5.03 (s, 2H), 3.78 (t, J=13.3 Hz, 2H), 3.56 (t, J=7.0 Hz, 2H), 2.56 (sept, J=7.2 Hz, 2H). LRMS(ESI): (calc.) 393.2 (found) 394.1 (MH) <sup>+</sup>	J, I, CC, K(with 322), G
	527			(S)-N-(4-aminobiphen-3-yl)-4-(3-fluoropyrrolidin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.45 (s, 1H), 7.89 (d, J=8.8 Hz, 2H), 7.54 (d, J=7.4 Hz, 2H), 7.50 (d, J=2.2 Hz, 1H), 7.38 (t, J=7.4 Hz, 2H), 7.29 (dd, J=8.2, 2.2 Hz, 1H), 7.22 (t, J=7.2 Hz, 1H), 6.85 (d, J=8.2 Hz, 1H), 6.63 (d, J=9.0 Hz, 2H), 5.47 (d, J=54.0 Hz, 1H), 5.02 (s, 2H), 3.66-3.48 (m, 3H), 3.49-3.36 (m, 1H), 2.29-2.16 (m, 2H). LRMS(ESI): (calc.) 375.2 (found) 376.2 (MH) <sup>+</sup>	J, I, F(with 322), G

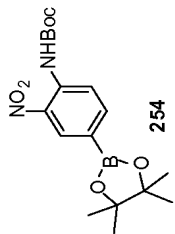
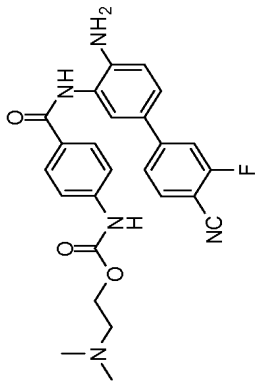
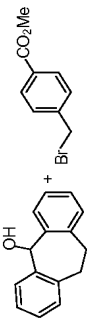
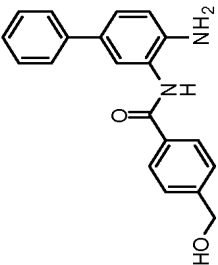
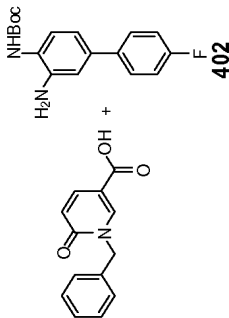
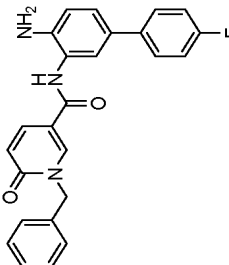
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	528			1-(4-(4-aminobiphenyl-3-yl)-3-phenylpiperidine-4-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 7.92 (d, J=8.8 Hz, 2H), 7.56 (d, J=7.4 Hz, 2H), 7.47 (d, J=1.2 Hz, 1H), 7.37 (t, J=7.4 Hz, 2H), 7.36 (d, J=8.0 Hz, 1H), 7.24 (t, J=7.2 Hz, 1H), 7.03 (d, J=8.8 Hz, 2H), 6.97 (d, J=8.4 Hz, 1H), 3.98 (d, J=13.2 Hz, 2H), 2.89 (t, J=11.3 Hz, 2H), 2.50-2.40 (m, 1H), 1.90 (d, J=13.5 Hz, 2H), 1.80 (qd, J=11.9, 3.7 Hz, 2H). LRMS(ESI): (calc.) 414.2 (found) 415.2 (MH) <sup>+</sup>	J, I, F(with 322), G
	529			N-(4-aminobiphenyl-3-yl)-4-(4-ethylpiperazin-1-yl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.50 (s, 1H), 7.88 (d, J=9.0 Hz, 2H), 7.54 (dd, J=7.0, 1.2 Hz, 2H), 7.49 (d, J=2.2 Hz, 1H), 7.37 (t, J=7.4 Hz, 2H), 7.29 (dd, J=8.2, 2.2 Hz, 1H), 7.22 (tt, J=7.4 Hz, 1.2 Hz, 1H), 7.00 (d, J=9.0 Hz, 2H), 6.85 (d, J=8.2 Hz, 1H), 5.03 (s, 2H), 3.30-3.20 (m, 4H), 2.41-2.30 (m, 2H), 1.03 (t, J=7.2 Hz, 3H). Signal for 4H overlapped with signal of DMSO LRMS(ESI): (calc.) 400.52 (found) 401.2 (MH) <sup>+</sup>	J, I, F(with 322), G

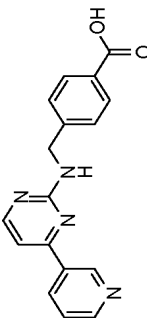
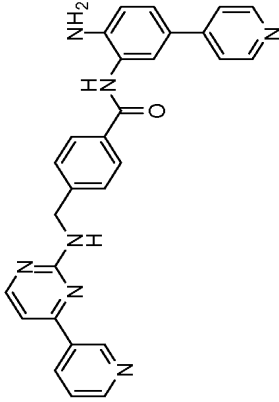
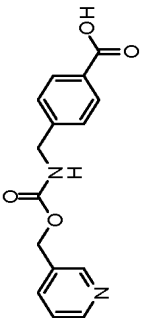
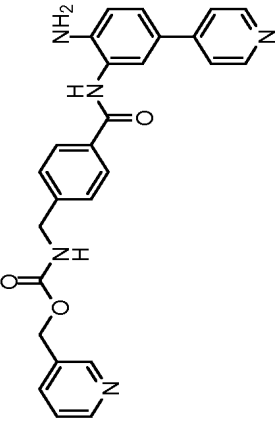
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	530			(S)-N-(4-aminobiphenyl-4-yl)-N-methylpyrrolidine-1-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 7.91 (d, J=8.8 Hz, 2H), 7.56 (dd, J=7.0, 1.4 Hz, 2H), 7.46 (d, J=2.0 Hz, 1H), 7.37 (t, J=7.0 Hz, 2H), 7.36 (dd, J=8.4, 2.0 Hz, 1H), 7.24 (tt, J=7.0, 1.4 Hz, 1H), 6.97 (d, J=8.4 Hz, 1H), 6.65 (d, J=9.0 Hz, 2H), 3.65 (dd, J=9.6, 7.2 Hz, 1H), 3.57 (t, J=8.2 Hz, 1H), 3.39 (td, J=10.0, 6.8 Hz, 1H), 3.22 (t, J=8.4 Hz, 1H), 3.00 (quint, J=8.8 Hz, 1H), 2.38 (s, 6H), 2.33 (m, 1H), 2.15-1.90 (m, 1H).LRMS(ESI): (calc.) 400.5 (found) 401.2 (MH) <sup>+</sup>	J, I, F(with 322), G
	531			N-(2-amino-5-(thiophen-2-yl)phenyl)-4-benzylpiperazine-1-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 7.40-7.28 (m, 7H), 7.24 (dd, J = 5.1, 1.2 Hz, 1H), 7.20 (dd, J = 3.5, 1.0 Hz, 1H), 7.05-7.02 (m, 1H), 6.85 (d, J = 8.2 Hz, 1H), 3.62-3.54 (m, 6H), 2.56-2.49 (m, 4H).LRMS(ESI): (calc.) 392.2 (found) 393.4 (MH) <sup>+</sup>	B, BB, FF

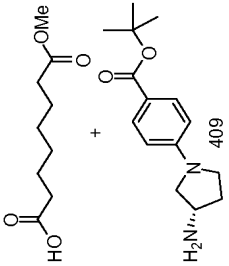
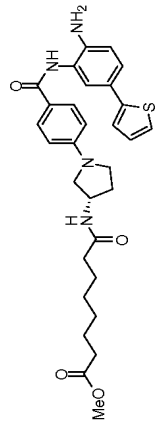
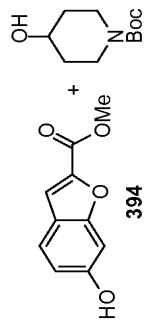
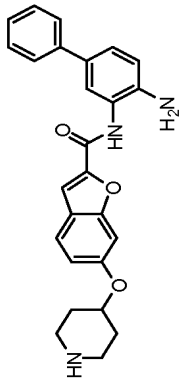
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	532			N-(4-aminobiphenyl-3-yl)-5-methoxypyridin-2-ylmethanimide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.72 (s, 1H), 8.82 (d, J=1.6 Hz, 1H), 8.26 (dd, J=8.6, 2.2 Hz, 1H), 7.55 - 7.50 (m, 3H), 7.40 - 7.31 (m, 3H), 7.23 (t, J=7.4 Hz, 1H), 6.93 (d, J=8.8 Hz, 1H), 5.12 (d, J=11.4 Hz, 2H), 3.92 (s, 3H). LRMS(ESI): (calc.) 319.1 (found) 320.3 (MH)+	F, G
	533			N-(4-aminobiphenyl-3-yl)-5-(morpholino(methyl)thio)pyridine-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 7.77 (d, J=3.3 Hz, 1H), 7.56 - 7.54 (m, 2H), 7.46 (d, J=2.2 Hz, 1H), 7.39 - 7.34 (m, 3H), 7.25 - 7.21 (m, 1H), 7.05 (d, J=3.5 Hz, 1H), 6.96 (d, J=8.4 Hz, 1H), 3.76 (s, 2H), 3.70 (t, J=4.5 Hz, 4H), 2.56 - 2.50 (m, 4H). LRMS: (calc.) 393.2 (found) 394.4 (MH)+	F, Z, G

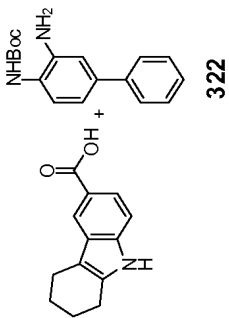
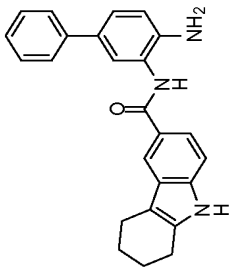
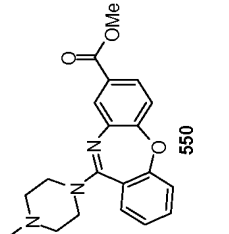
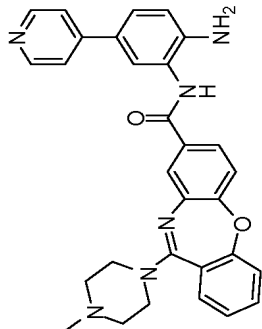
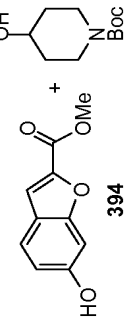
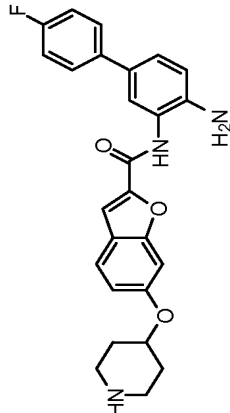
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	535			(R)-N-(4-aminobiphen-3-yl)-4-(3-(dimethylamino)pyrrolidin-1-yl)benzamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 7.91 (d, J=8.8 Hz, 2H), 7.56 (dd, J=8.2, 1.2 Hz, 2H), 7.46 (d, J=2.1 Hz, 1H), 7.37 (t, J=7.4 Hz, 2H), 7.36 (dd, J=8.2, 2.1 Hz, 1H), 7.24 (tt, J=7.4, 1.2 Hz, 1H), 6.97 (d, J=8.2 Hz, 1H), 6.67 (d, J=9.2 Hz, 2H), 3.72-3.65 (m, 1H), 3.65-3.55 (m, 1H), 3.45-3.25 (m, 3H), 2.55-2.45 (m, 6H), 2.45-2.34 (m, 1H), 2.05-1.95 (m, 1H). LRMS: (calc.): 400.2 (found) 401.3 (MH) <sup>+</sup>	J, I, F(with <b>322</b> ), G
	536			(R)-N-(4-aminobiphen-3-yl)-4-(3-(ethylamino)pyrrolidin-1-yl)benzamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 7.89 (d, J=8.8 Hz, 2H), 7.56 (dd, J=7.2, 1.2 Hz, 2H), 7.46 (d, J=2.2 Hz, 1H), 7.36 (t, J=7.8 Hz, 2H), 7.36 (dd, J=8.2, 2.2 Hz, 1H), 7.24 (t, J=7.3 Hz, 1H), 6.97 (d, J=8.4 Hz, 1H), 6.65 (d, J=8.8 Hz, 2H), 3.65 (dd, J=9.8, 6.4 Hz, 1H), 3.60-3.50 (m, 2H), 3.39 (q, J=7.4 Hz, 1H), 3.20 (dd, J=9.7, 6.0 Hz, 1H), 2.80-2.68 (m, 2H), 2.30 (sext, J=5.8 Hz, 1H), 1.95 (sext, J=5.7 Hz, 1H), 1.17 (t, J=5.3 Hz, 3H). LRMS: (calc.) 400.2 (found) 401.3 (MH) <sup>+</sup>	J, T, I, F(with <b>322</b> ), G, R

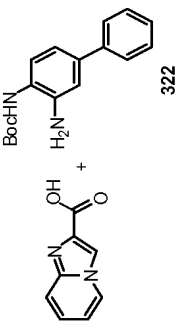
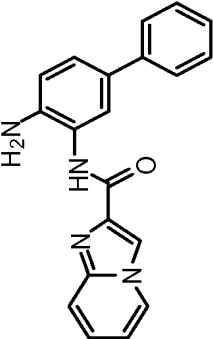
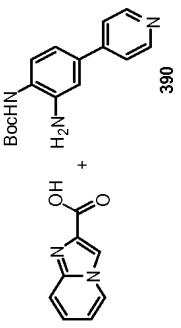
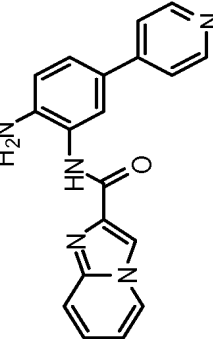
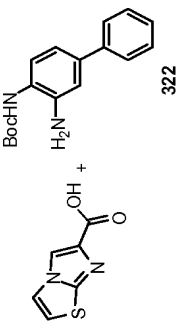
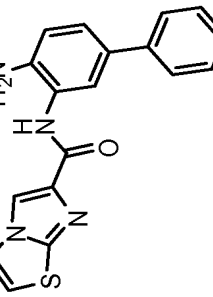


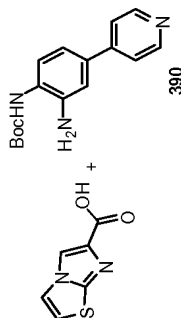
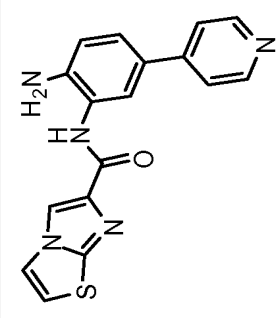
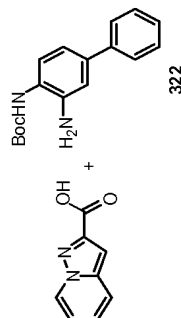
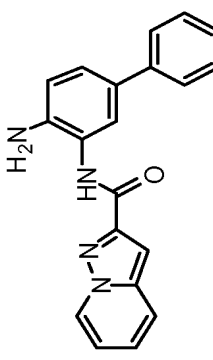
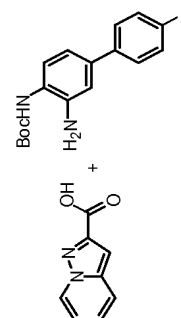
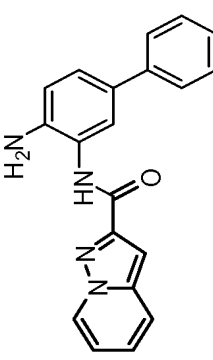
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	537			2-(dimethylamino)ethyl 4-(4-amino-4'-cyano-3'-fluorobiphenyl-3-ylcarbamoyl)phenylcarbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.02 (s, 1H), 9.62 (s, 1H), 7.95 (d, J=8.8 Hz, 2H), 7.89-7.86 (m, 1H), 7.73 (dd, J=11.6, 1.6 Hz, 1H), 7.67 (d, J=2.0 Hz, 1H), 7.63 (dd, J=8.4, 2.0 Hz, 1H), 7.60-7.58 (m, 2H), 7.51 (dd, J=8.4, 2.4 Hz, 1H), 6.87 (d, J=8.4 Hz, 1H), 5.46 (s, 2H), 4.19 (t, J=5.6 Hz, 2H), 2.51 (t, J=1.6 Hz, 2H, overlapped DMSO-d <sub>6</sub> ), 2.18 (s, 6H). LRMS: (calc.) 461.2 (found) 462.2 (MH) <sup>+</sup>	C, F (with 335), B, G
	538			N-(4-aminobiphenyl-3-yl)-4-(hydroxymethyl)benzamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.03 (d, J = 8.4 Hz, 2H), 7.64-7.51 (m, 5H), 7.47-7.37 (m, 3H), 7.32-7.24 (m, 1H), 7.01 (d, J = 8.2 Hz, 1H), 4.74 (s, 2H) LRMS: (calc.) 318.1 (found) 319.4 (MH) <sup>+</sup>	GG, P, F(with 322), G
	539			N-(4-amino-4'-fluorobiphenyl-3-yl)-1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.57 (d, J = 2.0 Hz, 1H), 8.12 (dd, J = 9.6, 2.3 Hz, 1H), 7.60-7.53 (m, 2H), 7.44-7.32 (m, 7H), 7.18-7.09 (m, 2H), 6.96 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 9.4 Hz, 1H), 5.29 (s, 2H). LRMS: (calc.) 413.1 (found) 414.4 (MH) <sup>+</sup>	F, G

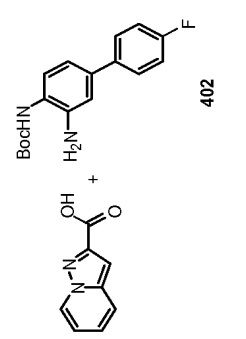
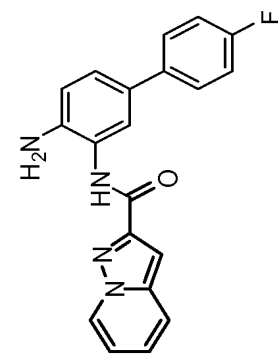
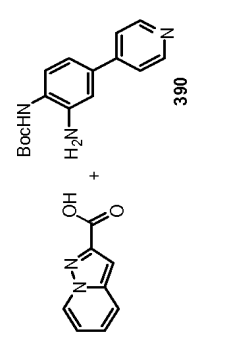
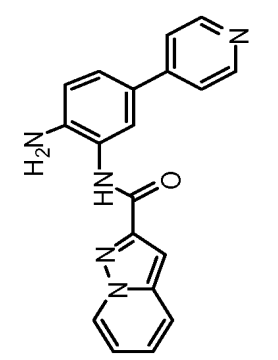
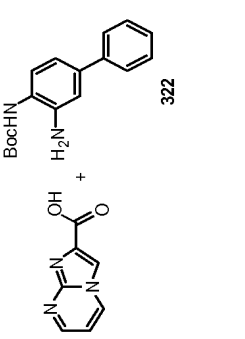
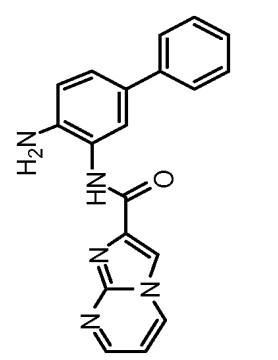
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	<b>540</b>	 <p>Described in US 2004/0142953</p>		N-(2-amino-5-((pyridin-4-yl)phenyl)-4-yl)pyrimidin-3-ylpyrimidin-2-ylamino)methylbenzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.66 (bs, 1H), 9.23 (bs, 1H), 8.66 (bs, 1H), 8.48 (d, J=6.0 Hz, 2H), 8.39 (d, J=5.2 Hz, 2H), 8.00 (t, J=6.0 Hz, 1H), 7.93 (d, J=8.0 Hz, 2H), 7.65 (bs, 1H), 7.55 (d, J=6.0 Hz, 2H), 7.50-7.46 (m, 4H), 7.25 (d, J=5.2 Hz, 1H), 6.85 (d, J=8.4 Hz, 1H), 5.32 (d, J=8.8 Hz, 2H), 4.64 (d, J=5.6 Hz, 2H). LRMS(ESI): (calc.) 473.2 (found) 474.2 (MH) <sup>+</sup>	F(with <b>390</b> ), G
	<b>541</b>	 <p>Described in <i>J. Med. Chem.</i> <b>1999</b>, 42, 3001-3003.</p>		pyridin-3-ylmethyl 4-((2-amino-5-((pyridin-4-yl)phenyl)carbamoyl)benzyl)carbamate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.72 (s, 1H), 8.57 (s, 1H), 8.51 (dd, J=1.6, 4.8 Hz, 1H), 8.49 (dd, J=1.6, 4.8 Hz, 2H), 7.98-7.95 (m, 1H), 7.94 (d, J=8.4 Hz, 2H), 7.77 (bd, J=8.0 Hz, 1H), 7.65 (d, J=2.0 Hz, 1H), 7.56 (dd, J=1.6, 4.4 Hz, 2H), 7.49 (dd, J=2.4, 8.4 Hz, 1H), 7.41-7.37 (m, 1H), 7.36 (d, J=8.4 Hz, 2H), 6.87 (d, J=8.4 Hz, 1H), 5.35 (bs, 2H), 5.08 (bs, 2H), 4.26 (d, J=6.0 Hz, 2H). LRMS: (calc.) 453.2 (found) 454.2 (MH) <sup>+</sup>	F(with <b>390</b> ), G

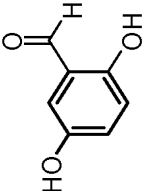
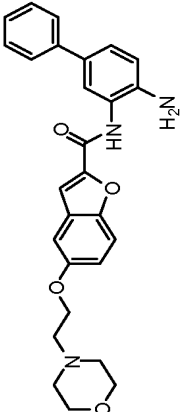
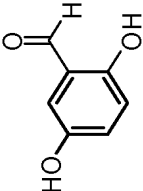
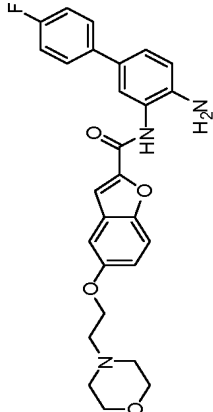
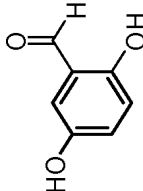
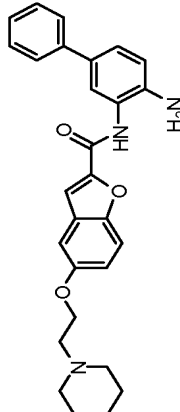
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	542			(S)-methyl 8-((1-(4-(2-amino-5-(thiophen-2-yl)phenylcarbonyl)phenyl)amoyl)phenyl)pyrrolidin-3-yl)amino)-8-oxooctanoate	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.42 (s, 1H), 8.11 (d, J=6.4Hz, 1H), 7.87 (d, J=8.8Hz, 2H), 7.45 (d, J=2.2Hz, 1H), 7.34 (d, J=5.1Hz, 1H), 7.27 to 7.22 (m, 2H), 7.04 to 7.02 (m, 1H), 6.79 (d, J=8.4Hz, 1H), 6.57 (d, J=8.8Hz, 2H), 5.06 (s, 2H), 4.38 to 4.37 (m, 1H), 3.56 (s, 3H), 3.42 to 3.27 (m, 2H), 3.13 to 3.10 (m, 1H), 2.26 (t, J=7.4Hz, 2H), 2.19-2.15 (m, 1H), 2.05 (t, J=7.2Hz, 2H), 1.89-1.88 (m, 1H), 1.48-1.47 (m, 4H), 1.23-1.22 (m, 5H). LRMS(ESI): (calc.) 548.3 (found) 549.3 (MH) <sup>+</sup>	F, I, F(with 4), G
	543			N-(4-aminobiphenyl-3-yl)-6-(piperidin-4-yloxy)benzofuran-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.45 (s, 1H), 7.64 (d, J=8.8 Hz, 1H), 7.57 - 7.54 (m, 4H), 7.37 (t, J=7.0 Hz, 3H), 7.29 (s, 1H), 7.24 (t, J=7.2 Hz, 1H), 7.05 (dd, J=8.6, 2.0 Hz, 1H), 6.98 (d, J=8.2 Hz, 1H), 4.79 - 4.77 (m, 1H), 3.44 - 3.37 (m, 2H), 3.25 - 3.19 (m, 2H), 2.23 - 2.17 (m, 2H), 2.09 - 2.03 (m, 2H). LRMS: (calc.) 427.2 (found) 428.5 (MH) <sup>+</sup>	HH, P, F(with 322), G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	544	 322		N-(4-aminobiphenyl-3-yl)-2,3,4,9-tetrahydro-1H-carbazole-6-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.18 (s, 1H), 7.79-7.72 (m, 1H), 7.64-7.58 (m, 2H), 7.55 (s, 1H), 7.44-7.34 (m, 4H), 7.31-7.23 (m, 1H), 7.06-7.00 (m, 1H), 2.84-2.77 (m, 4H), 2.02-1.89 (m, 4H). LRMS: (calc.) 381.2 (found) 382.5 (MH)+	F, G
	552	 550		(E)-N-(2-amino-5-(pyridin-4-yl)phenyl)-11-(4-methylpiperazin-1-yl)dibenzo[b,f][1,4]oxazepine-8-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.39 (d, J=6.0 Hz, 2H), 7.75 (d, J=2.4 Hz, 1H), 7.63 - 7.19 (m, 10H), 6.92 (d, J=8.4 Hz, 1H), 3.53 (br s, 4H), 2.51 (br s, 4H), 2.30 (s, 3H). LRMS: (calc.) 504.2 (found) 505.3 (MH)+	P, F(with 390), G
	553	 394		N-(4-amino-4'-fluorobiphenyl-3-yl)-6-(piperidin-4-yl)oxybenzofuran-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.54 (br s, 1H), 7.62 (d, J=8.6 Hz, 1H), 7.55 - 7.50 (m, 4H), 7.32 (dd, J=8.4, 2.4 Hz, 1H), 7.27 (d, J=1.5 Hz, 1H), 7.12 - 7.01 (m, 3H), 6.96 (d, J=8.4 Hz, 1H), 4.77 - 4.74 (m, 1H), 3.43 - 3.46 (m, 2H), 3.24 - 3.28 (m, 2H), 2.22 - 2.15 (m, 2H), 2.09 - 2.01 (m, 2H). LRMS(ESI): (calc.) 445.2 (found) 446.5 (MH)+	HH, P, F(with 402), G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	554			N-(4-aminobiphen-3-yl)imidazo[1,2-a]pyridine-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.55 (d, J = 6.7 Hz, 1H), 8.46 (s, 1H), 7.79 (s, 1H), 7.68 (d, J = 9.4 Hz, 1H), 7.61 (d, J = 7.8 Hz, 2H), 7.49-7.37 (m, 4H), 7.32-7.25 (m, 1H), 7.08-6.99 (m, 2H). LRMS: calc. 328.1, found 329.4.	F, G
	555			N-(2-amino-5-(pyridin-4-yl)phenyl)imidazo[1,2-a]pyridine-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.84 (s, 1H), 8.67 (d, J = 6.8 Hz, 1H), 8.57 (s, 3H), 7.95 (s, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.63 (d, J = 5.3 Hz, 2H), 7.52 (d, J = 8.2 Hz, 1H), 7.43 (t, J = 8.2 Hz, 1H), 7.07 (t, J = 6.7 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 5.39 (s, 2H). LRMS: calc. 329.1, found 330.4.	F, G
	556			N-(4-aminobiphen-3-yl)imidazo[2,1-b]thiazole-6-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.61 (s, 1H), 8.38 (s, 1H), 8.04 (d, J = 4.5 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.62-7.57 (m, 2H), 7.49-7.41 (m, 3H), 7.35-7.26 (m, 2H), 6.92 (d, J = 8.7 Hz, 1H), 5.10 (s, 2H). LRMS: calc. 334.1, found 335.4.	F, G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	557	 390		N-(2-amino-5-(pyridin-4-yl)phenyl)imidoazo[2,1-b]thiazole-6-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.63 (s, 1H), 8.55 (s, 2H), 8.39 (s, 1H), 8.06-8.00 (m, 1H), 7.94-7.88 (m, 1H), 7.64-7.57 (m, 2H), 7.53-7.44 (m, 2H), 6.94 (d, J = 5.0 Hz, 1H), 5.37 (s, 2H). LRMS: calc. 335.1, found 336.4.	F, G
	558	 322		N-(4-aminobiphenyl-3-yl)pyrazolo[1,5-a]pyridine-2-carboxamide	<sup>1</sup> H NMR (MeOD-d <sub>4</sub> ) δ (ppm): 8.72-8.67 (m, 1H), 7.78 (dt, J = 9.0, 1.2 Hz, 1H), 7.70 (d, J = 2.2 Hz, 1H), 7.62 (d, J = 1.2 Hz, 1H), 7.60 (d, J = 1.2 Hz, 1H), 7.44-7.39 (m, 3H), 7.35-7.25 (m, 2H), 7.18 (d, J = 0.8 Hz, 1H), 7.09-7.01 (m, 2H). LRMS: calc. 328.1, found 329.5.	F, G
	559	 402		N-(4-aminobiphenyl-3-yl)pyrazolo[1,5-a]pyridine-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.81 (s, 1H), 8.80 (dd, J = 7.0, 1.0 Hz, 1H), 7.90-7.85 (m, 1H), 7.70 (d, J = 2.2 Hz, 1H), 7.66-7.59 (m, 2H), 7.40-7.23 (m, 4H), 7.17 (d, J = 0.6 Hz, 1H), 7.14-7.09 (m, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.15 (s, 2H). LRMS: calc. 346.2, found 347.5.	F, G

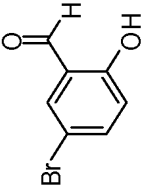
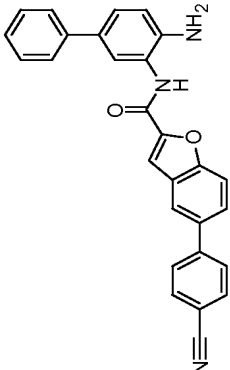
Ex	Cp d	Starting material	Structure	Name	Characterization	Preparative sequence
	560	 <chem>O=C(O)c1c[nH]c2ccccc12</chem> + <chem>CC(C)(C)Nc1ccc(NC(=O)c2c[nH]c3ccccc23)cc1</chem> 402	 <chem>Nc1ccc(NC(=O)c2c[nH]c3ccccc23)cc1</chem>	N-(4-amino-2-(4-fluorophenyl)phenyl)-1H-indazole-3-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.81 (s, 1H), 8.80 (dd, J = 7.0, 1.0 Hz, 1H), 7.90-7.85 (m, 1H), 7.70 (d, J = 2.2 Hz, 1H), 7.66-7.59 (m, 2H), 7.40-7.23 (m, 4H), 7.17 (d, J = 0.6 Hz, 1H), 7.14-7.09 (m, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.15 (s, 2H). LRMS: calc. 346.1, found 347.5.	F, G
	561	 <chem>O=C(O)c1c[nH]c2ccccc12</chem> + <chem>CC(C)(C)Nc1ccc(NC(=O)c2c[nH]c3ccccc23)cc1</chem> 390	 <chem>Nc1ccc(NC(=O)c2c[nH]c3ccccc23)cc1</chem>	N-(2-amino-5-(pyridin-4-yl)phenyl)-1H-indazole-3-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.84 (s, 1H), 8.80 (dd, J = 7.0, 0.8 Hz, 1H), 8.56 (dd, J = 4.7, 1.6 Hz, 2H), 7.90-7.85 (m, 2H), 7.66-7.60 (m, 2H), 7.54 (dd, J = 8.4, 2.2 Hz, 1H), 7.40-7.35 (m, 1H), 7.18 (s, 1H), 7.15-7.10 (m, 1H), 6.95 (d, J = 8.4 Hz, 1H), 5.42 (s, 2H). LRMS: calc. 329.1, found 330.4..	F, G
	562	 <chem>O=C(O)c1c[nH]c2ccccc12</chem> + <chem>CC(C)(C)Nc1ccc(NC(=O)c2c[nH]c3ccccc23)cc1</chem> 322	 <chem>Nc1ccc(NC(=O)c2c[nH]c3ccccc23)cc1</chem>	N-(4-aminobiphenyl-3-yl)-2-imidazo[1,2-a]pyrimidine-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.95 (br s, 1H), 9.80 (dd, J = 6.8, 2.2 Hz, 1H), 8.80-8.74 (m, 2H), 7.63-7.59 (m, 2H), 7.56 (d, J = 2.2 Hz, 1H), 7.46-7.38 (m, 3H), 7.34 (dd, 7.0, 4.3 Hz, 1H), 7.31-26 (m, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.28 (s, 2H). LRMS: calc. 329.1, found 330.4..	F, G

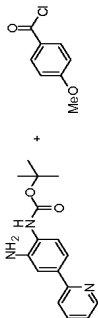
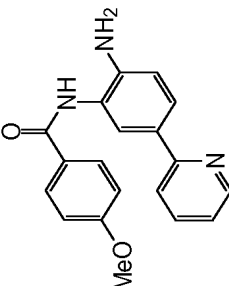
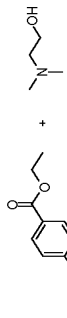
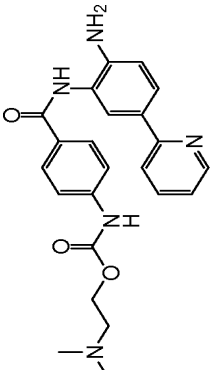
Ex	Cp <sub>d</sub>	Starting material	Structure	Name	Characterization	Preparative sequence
	563			N-(4-aminobiphenyl-3-yl)-5-(2-morpholinoethoxy)benzofuran-2-carboxamide	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 7.58 - 7.54 (m, 5H), 7.41 - 7.36 (m, 3H), 7.28 - 7.22 (m, 2H), 7.13 (dd, J=9.0, 2.6 Hz, 1H), 6.99 (d, J=8.4 Hz, 1H), 4.20 (t, J=5.5 Hz, 2H), 3.73 (t, J=4.7 Hz, 4H), 2.85 (t, J=5.5 Hz, 2H), 2.63 (t, J=4.7 Hz, 4H). . LRMS: calc. 457.2, found 458.5.	Q, S, P, N (with 322), G
	564			N-(4-amino-4'-fluorobiphenyl-3-yl)-5-(2-morpholinoethoxy)benzofuran-2-carboxamide	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 7.59 - 7.51 (m, 5H), 7.35 (dd, J=8.4, 2.2 Hz, 1H), 7.28 (d, J=2.3 Hz, 1H), 7.15 - 7.09 (m, 3H), 6.98 (d, J=8.2 Hz, 1H), 4.20 (t, J=5.4 Hz, 2H), 3.73 (t, J=4.7 Hz, 4H), 2.85 (t, J=5.5 Hz, 2H), 2.63 (t, J=4.5 Hz, 4H). LRMS: calc. 475.2, found 476.3. Do not fit with the structure	Q, S, P, N (with 402), G
	565			N-(4-aminobiphenyl-3-yl)-5-(2-(piperidin-1-yl)ethoxy)benzofuran-2-carboxamide	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 7.57 - 7.53 (m, 5H), 7.40 - 7.35 (m, 3H), 7.27 - 7.22 (m, 2H), 7.12 (dd, J=9.0, 2.5 Hz, 1H), 6.98 (d, J=8.4 Hz, 1H), 4.18 (t, J=5.5 Hz, 2H), 2.82 (t, J=5.5 Hz, 2H), 2.58 (br s, 4H), 1.65 (q, J=5.7 Hz, 4H), 1.51 - 1.49 (m, 2H). LRMS: calc. 455.2, found 456.4	Q, S, P, N (with 322), G

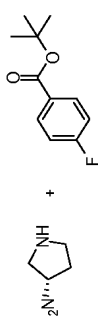
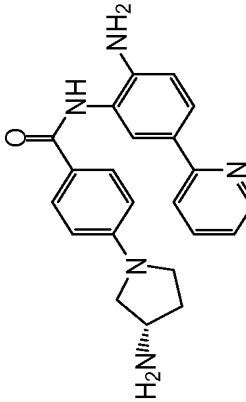


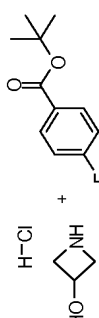
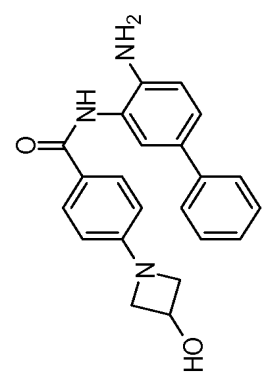
Ex	Cp d	Starting material	Structure	Name	Characterization	Preparative sequence
	566			N-(4-amino-4'-fluorobiphenyl-5-yl-3-yl)-5-(2-(piperidin-1-yl)ethoxy)benzofuran-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.92 (s, 1H), 7.62 (s, 1H), 7.58 - 7.54 (m, 3H), 7.48 (d, J=1.5 Hz, 1H), 7.31 - 7.28 (m, 2H), 7.18 (t, J=8.8 Hz, 2H), 7.06 (dd, J=9.0, 2.4 Hz, 1H), 6.84 (d, J=8.4 Hz, 1H), 5.15 (s, 2H), 4.09 (t, J=5.9 Hz, 2H), 2.66 (t, J=6.0 Hz, 2H), 2.43 (m, 4H), 1.50 - 1.45 (m, 4H), 1.38 - 1.36 (m, 2H). LRMS: calc. 473.2, found 474.3	Q, S, P, N (with 402), G
	567			N-(4-aminobiphenyl-3-yl)-5-methoxy-7-(morpholinomethyl)benzofuran-2-carboxamide	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 7.60 - 7.55 (m, 4H), 7.41 - 7.35 (m, 3H), 7.27 - 7.22 (m, 1H), 7.19 (d, J=2.5 Hz, 1H), 7.11 (d, J=2.5 Hz, 1H), 6.99 (d, J=8.4 Hz, 1H), 3.92 (s, 2H), 3.86 (s, 3H), 3.72 (t, J=4.5 Hz, 4H), 2.60 - 2.58 (m, 4H). LRMS: calc. 457.2, found 458.5	Q, S, P, N (with 322), G
	568			N-(4-amino-4'-fluorobiphenyl-5-yl-3-yl)-5-(2-(piperidin-1-yl)ethoxy)benzofuran-2-carboxamide	<sup>1</sup> H NMR (CD <sub>3</sub> OD) δ (ppm): 7.59 - 7.55 (m, 4H), 7.36 (dd, J=8.4, 1.7 Hz, 1H), 7.19 (d, J=2.2 Hz, 1H), 7.14 - 7.09 (m, 3H), 6.98 (d, J=8.4 Hz, 1H), 3.92 (s, 2H), 3.86 (s, 3H), 3.72 (t, J=4.5 Hz, 4H), 2.59 - 2.58 (m, 4H). LRMS: calc. 475.5, found 476.6	Q, S, P, N (with 402) G

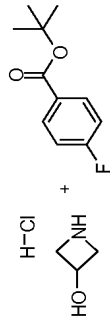
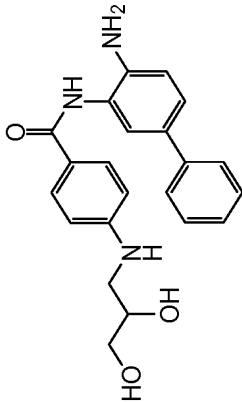
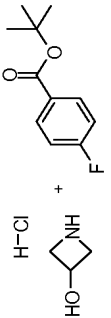
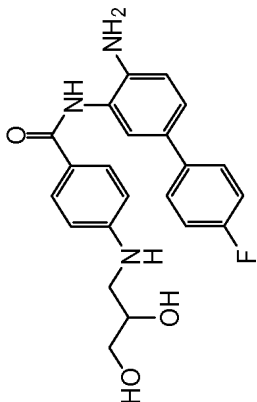
Ex	Cp d	Starting material	Structure	Name	Characterization	Preparative sequence
	569			N-(4-aminobiphenyl-3-yl)-7-methoxy-5-(morpholino methyl)benzo furan-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.91 (s, 1H), 7.69 (s, 1H), 7.56 - 7.52 (m, 3H), 7.41 - 7.33 (m, 3H), 7.28 - 7.21 (m, 2H), 7.04 (s, 1H), 6.87 (d, J=8.4 Hz, 1H), 5.16 (s, 2H), 3.98 (s, 3H), 3.60 - 3.54 (m, 6H), 2.39 (br s, 4H). LRMS: calc. 457.2, found 458.6	Q, S, P, N (with 322), G
	570			N-(4-amino-4'-fluorobiphenyl-3-yl)-7-methoxy-5-(morpholino methyl)benzo furan-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.89 (s, 1H), 7.68 (s, 1H), 7.57 (dd, J=8.8, 5.5 Hz, 2H), 7.49 (d, J=2.1 Hz, 1H), 7.31 (dd, J=8.2, 2.0 Hz, 1H), 7.27 (s, 1H), 7.21 (t, J=8.8 Hz, 2H), 7.03 (s, 1H), 6.86 (d, J=8.2 Hz, 2H), 3.97 (s, 3H), 3.59 (t, J=3.9 Hz, 4H), 3.55 (s, 2H), 2.40 - 2.36 (m, 4H). LRMS: calc. 475.5, found 476.6	Q, S, P, N (with 402), G
	571			N-(2-amino-5-(pyridin-4-yl)phenyl)-4-((6,7,8,9,10,11-hexahydro-5H-cycloocta[b]indol-5-yl)methyl)benzamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 9.58 (s, 1H), 8.48 (d, J=6.3 Hz, 2H), 7.62 - 7.44 (m, 7H), 7.24 - 7.21 (m, 3H), 6.84 (d, J=8.4 Hz, 1H), 6.71 (d, J=8.2 Hz, 2H), 5.31 (s, 2H), 3.19 (q, J=8.7 Hz, 2H), 2.95 - 2.91 (m, 1H), 2.67 - 2.61 (m, 1H), 2.48 - 2.44 (m, 1H), 2.24 - 2.20 (m, 1H), 2.08 - 2.06 (m, 1H), 1.78 - 1.27 (m, 5H), 0.77 - 0.73 (m, 2H). LRMS: (calc.) 500.6 (found) 501.5 (MH) <sup>+</sup>	D (with NaH), P, F (with 390), G,

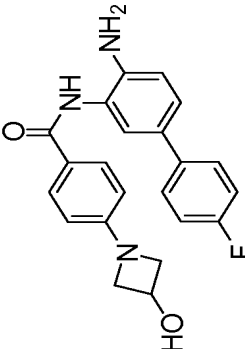
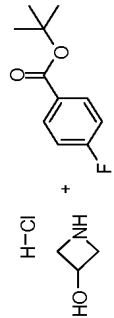
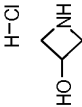
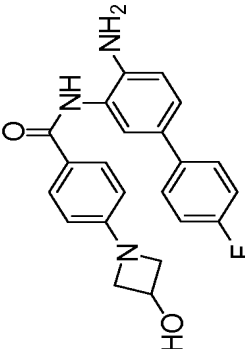
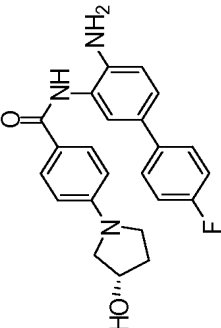
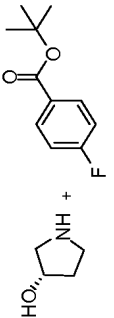
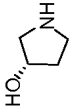
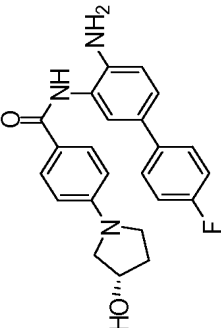
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	572			N-(4-aminobiphen-5-yl)-5-(4-cyanophenyl)-2-benzofuran-2-carboxamide	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) δ (ppm): 10.05 (s, 1H), 8.22 (d, J=1.2 Hz, 1H), 7.96 (s, 4H), 7.89 - 7.81 (m, 3H), 7.57 - 7.53 (m, 3H), 7.41 - 7.34 (m, 3H), 7.26 - 7.22 (m, 1H), 6.88 (d, J=8.4 Hz, 1H), 5.20 (s, 2H). LRMS: (calc.) 429.2 (found) 430.5 (MH) <sup>+</sup>	Q, P, N (with 322), B, G

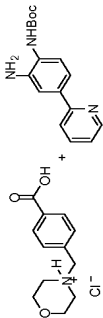
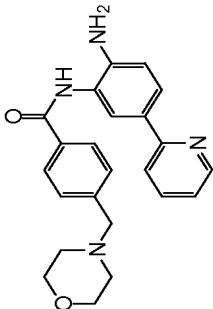
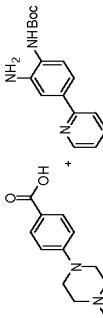
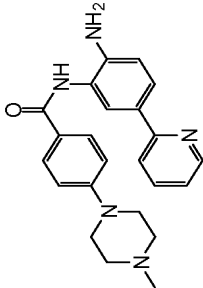
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	573			N-(2-amino-5-(pyridin-2-yl)phenyl)-4-methoxybenzamide	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.65 (s, 1H), 8.52 (m, 1H), 8.01 (d, J = 5.8 Hz, 2H), 7.92 (m, 1H), 7.73 (m, 3H), 7.18 (m, 1H), 7.13 (d, J = 5.7 Hz, 2H), 6.81 (d, J = 5.2 Hz, 1H), 5.23 (s, 1H), 3.83 (s, 3H). MS (m/z): 320.2 (M+H).	K, G
	574			2-(dimethylamino)ethyl 4-(2-amino-5-(pyridin-2-yl)phenyl)carbamate	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 10.01 (s, 1H), 9.62 (s, 1H), 8.52 (m, 1H), 7.95 (m, 3H), 7.76 (m, 3H), 7.58 (d, J = 8.2 Hz, 2H), 7.18 (m, 1H), 6.84 (d, J = 8.1 Hz, 1H), 5.23 (s, 2H), 4.19 (t, J = 5.2 Hz, 2H), 2.51 (t, J = 5.1 Hz, 2H), 2.18 (s, 6H). MS (m/z): 420.2 (M+H).	X, E, F, G

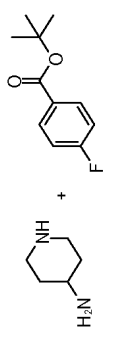
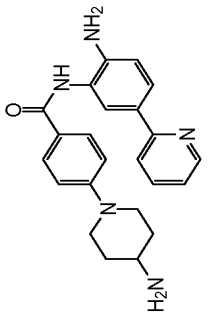
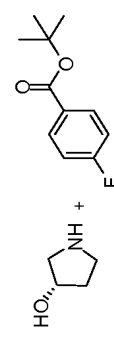
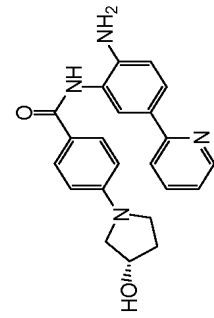
Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	<b>575</b>			2-(dimethylamino)ethyl 4-(2-amino-5-(pyridin-2-yl)phenyl)benzoyl carbamate	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.47 (s, 1H), 8.51 (d, J = 3.6 Hz, 1H), 7.94 (d, J = 2.2 Hz, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.76 (m, 2H), 7.70 (m, 1H), 7.18 (m, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.54 (d, J = 8.1 Hz, 2H), 5.21 (s, 2H), 3.62 (m, 1H), 3.48 (m, 3H), 3.30 (m, 2H), 3.05 (m, 1H), 2.11 (m, 1H), 1.80 (m, 1H). MS (m/z): 374.1 (M+H).	J, T, I, F, R, G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	<b>576</b>			N-(4-aminobiphenyl-3-yl)-4-(3-(hydroxyazetidin-1-yl)benzamide	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.47 (s, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.55 (dd, J = 8.4, 1.2 Hz, 2H), 7.49 (d, J = 2.0 Hz, 1H), 7.39 (tt, J = 7.8, 1.8 Hz, 2H), 7.30 (dd, J = 8.2, 2.2 Hz, 1H), 7.24 (tt, J = 7.4, 1.1 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 8.8 Hz, 2H), 5.71 (d, J = 6.0 Hz, 1H), 5.03 (bs, 2H), 4.61 (sext, J = 5.3 Hz, 1H), 4.15 (t, J = 7.6 Hz, 2H), 3.61 (dd, J = 8.4, 4.8 Hz, 2H). MS (m/z): 360.2 (M+H).	J, V, I, F, O, G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	577			N-(4-aminobiphenyl-3-yl)-4-(2,3-dihydroxypropyl)benzamide	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) $\delta$ (ppm): 9.36 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.55 (dd, J = 8.4, 0.8 Hz, 2H), 7.50 (d, J = 2.0 Hz, 1H), 7.39 (t, J = 7.8 Hz, 2H), 7.29 (dd, J = 8.4, 2.0 Hz, 1H), 7.24 (tt, J = 7.4, 1.1 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 8.8 Hz, 2H), 6.19 (t, J = 5.8 Hz, 1H), 5.02 (bs, 2H), 4.84 (d, J = 5.2 Hz, 1H), 4.65 (t, J = 5.8 Hz, 1H), 3.65 (sext, J = 5.5 Hz, 1H), 3.39 (m, 2H), 3.24 (m, 1H), 2.99 (m, 1H). MS (m/z): 378.5 (M+H).	J, V, I, F, O, G
	578			N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(2,3-dihydroxypropyl)benzamide	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) $\delta$ (ppm): 9.36 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.57 (t, J = 6.6 Hz, 2H), 7.47 (s, 1H), 7.23 (m, 3H), 6.84 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 8.4 Hz, 2H), 6.20 (t, J = 5.4 Hz, 1H), 5.03 (bs, 2H), 4.85 (d, J = 4.4 Hz, 1H), 4.66 (t, J = 5.2 Hz, 1H), 3.65 (q, J = 4.4 Hz, 1H), 3.39 (m, 2H), 3.24 (m, 1H), 2.98 (m, 1H). MS (m/z): 396.1 (M+H).	J, V, I, F, O, G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	579	  		N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(3-hydroxypropyl)-1-benzamide	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) $\delta$ (ppm): 9.46 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.57 (dd, J = 8.2, 5.4 Hz, 2H), 7.47 (bs, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 8.8 Hz, 2H), 6.85 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 8.4 Hz, 2H), 5.71 (d, J = 6.8 Hz, 1H), 5.04 (s, 2H), 4.61 (sext, J = 5.5 Hz, 1H), 4.15 (t, J = 7.0 Hz, 2H), 3.61 (dd, J = 7.8 Hz, 2H). MS (m/z): 378.1 (M+H).	J, V, I, F, O, G
	580	  		(S)-N-(4-amino-4'-fluorobiphenyl-3-yl)-4-(3-hydroxypropyl)-1-benzamide	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) $\delta$ (ppm): 9.42 (s, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.58 (dd, J = 8.6, 5.4 Hz, 2H), 7.48 (d, J = 1.6 Hz, 1H), 7.27 (dd, J = 8.4 Hz, 1H), 7.21 (t, J = 8.8 Hz, 2H), 6.85 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 8.4 Hz, 2H), 5.03 (bs, 2H), 5.02 (s, 1H), 4.43 (bs, 1H), 3.47 (dd, J = 10.6, 4.6 Hz, 1H), 3.37 (m, 2H), 3.17 (d, J = 10.4 Hz, 1H), 2.06 (m, 1H), 1.93 (m, 1H). MS (m/z): 392.2 (M+H).	J, I, F, G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	581			N-(2-amino-5-((pyrididin-2-yl)phenyl)-4-(morpholino)methyl)benzamide	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.74 (s, 1H), 8.54 (d, J = 4.8 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.97 (s, 1H), 7.76 (m, 3H), 7.45 (d, J = 8.0 Hz, 2H), 7.19 (m, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.28 (s, 2H), 3.59 (t, J = 4.4 Hz, 4H), 3.55 (s, 2H), 2.38 (bs, 4H). MS (m/z): 389.5 (M+H).	F, G
	582			N-(2-amino-5-((pyrididin-2-yl)phenyl)-4-(4-methylpiperazin-1-yl)methyl)benzamide	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.55 (s, 1H), 8.54 (dt, J = 4.8, 1.4 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.75 (m, 3H), 7.18 (m, 1H), 7.01 (d, J = 9.2 Hz, 2H), 6.85 (d, J = 8.4 Hz, 1H), 5.22 (s, 2H), 3.28 (t, J = 5.0 Hz, 4H), 2.45 (t, J = 5.0 Hz, 4H), 2.23 (s, 3H). MS (m/z): 388.1 (M+H).	F, G

Ex	Cpd	Starting material	Structure	Name	Characterization	Preparative sequence
	583			N-(2-amino-5-(pyridin-2-yl)phenyl)-4-(4-aminopiperidin-1-yl)benzamide	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.51 (s, 1H), 8.54 (dt, J = 4.5, 1.3 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.68 (m, 2H), 7.73 (dd, J = 8.4, 2.0 Hz, 1H), 7.18 (m, 1H), 6.99 (d, J = 9.2 Hz, 2H), 6.85 (d, J = 8.4 Hz, 1H), 5.21 (s, 2H), 3.82 (d, J = 13.2 Hz, 2H), 2.86 (td, J = 12.2, 2.4 Hz, 2H), 2.77 (m, 1H), 1.77 (dd, J = 12.8, 3.2 Hz, 2H), 1.27 (m, 2H). MS (m/z): 388.1 (M+H).	J, T, I, F, R, G
	584			(S)-N-(2-amino-5-(pyridin-2-yl)phenyl)-4-(3-hydroxypyrrolidin-1-yl)benzamide	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ (ppm): 9.46 (s, 1H), 8.54 (dt, J = 4.5, 1.3 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.77 (m, 2H), 7.72 (dd, J = 8.4, 2.4 Hz, 1H), 7.18 (ddd, J = 6.1, 4.7, 2.3 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 8.8 Hz, 2H), 5.20 (bs, 2H), 5.03 (d, J = 3.6 Hz, 1H), 4.43 (bs, 1H), 3.47 (dd, J = 10.4, 4.8 Hz, 1H), 3.39 (m, 2H), 3.17 (d, J = 10.4 Hz, 1H), 2.06 (m, 1H), 1.93 (m, 1H). MS (m/z): 375.1 (M+H).	J, I, F, G



## ASSAY EXAMPLES

### Assay Example 1

#### Inhibition of Histone Deacetylase Enzymatic (HDAC-1) Activity

[1064] The following protocol was used to assay the compounds of the invention. In the assay, the buffer used was 25mM HEPES, pH 8.0, 137mM NaCl, 2.7mM KCl, 1mM MgCl<sub>2</sub> and the substrate was Boc-Lys(Ac)-AMC in a 50mM stock solution in DMSO. The enzyme stock solution was 4.08 µg/mL in buffer.

[1065] The compounds were pre-incubated (2µl in DMSO diluted to 13 µl in buffer for transfer to assay plate) with enzyme (20µl of 4.08µg/ml) for 10 minutes at room temperature (35µl pre-incubation volume). The mixture was pre-incubated for 5 minutes at room temperature. The reaction was started by bringing the temperature to 37°C and adding 15 µl substrate. Total reaction volume was 50 µl. The reaction was stopped after 20 minutes by addition of 50µl developer, prepared as directed by Biomol (Fluor-de-Lys developer, Cat. # KI-105). A plate was incubated in the dark for 10 minutes at room temperature before reading ( $\lambda_{\text{Ex}}$ =360nm,  $\lambda_{\text{Em}}$ =470nm, Cutoff filter at 435nm).

[1066] Table 21 below displays comparative data for the compounds of the invention demonstrating the increased HDAC-1 inhibitory activity resulting from incorporating a planar substituent.

### Assay Example 2

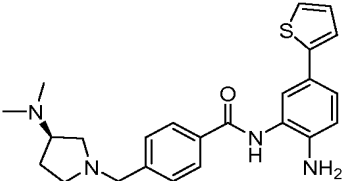
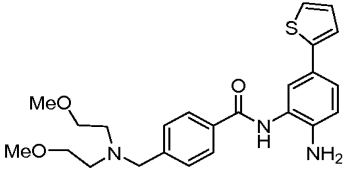
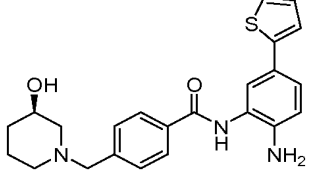
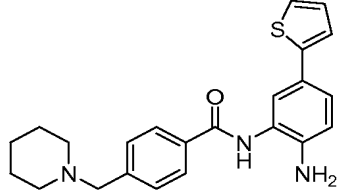
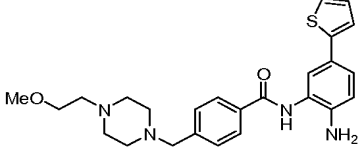
#### MTT Assay

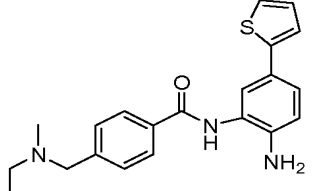
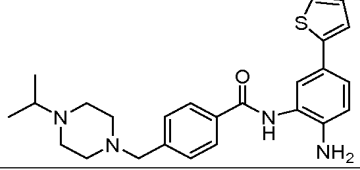
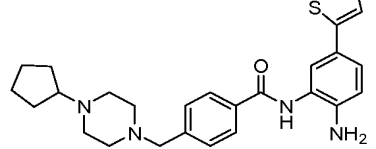
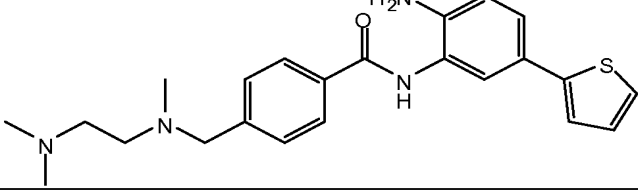
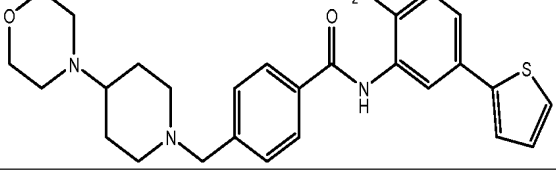
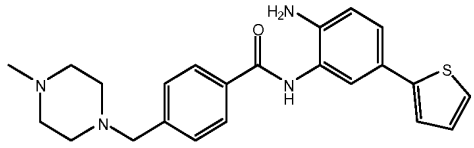
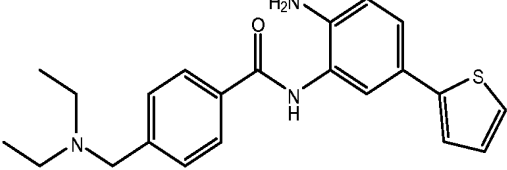
[1067] Compounds at various concentrations were added to human colon cancer HCT116 cells plated in 96-well plates. Cells were incubated for 72 hours at 37°C in 5% CO<sub>2</sub> incubator. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide, Sigma) was added at a final concentration of 0.5 mg/ml and incubated with the cells for 4 hours before an equal volume of solubilization buffer (50% N,N-dimethylformamide, 20% SDS, pH 4.7) was added onto cultured cells. After overnight incubation, solubilized dye was quantified by colorimetric reading at 570 nM using a reference at 630 nM. OD values were converted to cell numbers according to a standard growth curve of the relevant cell line. The concentration which reduces cell numbers to 50% of those of DMSO-treated cells is determined as MTT IC<sub>50</sub>.

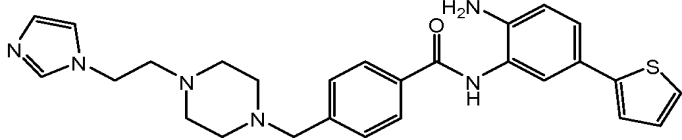
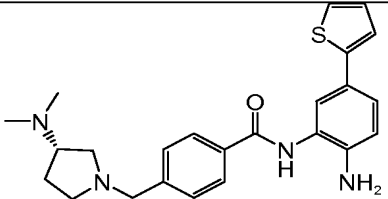
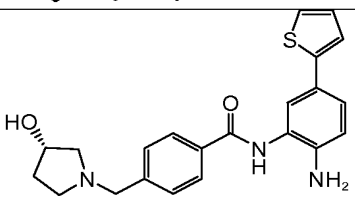
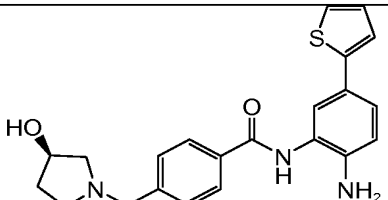
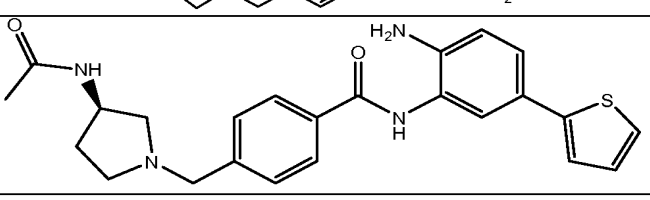
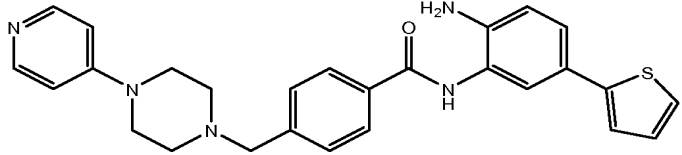
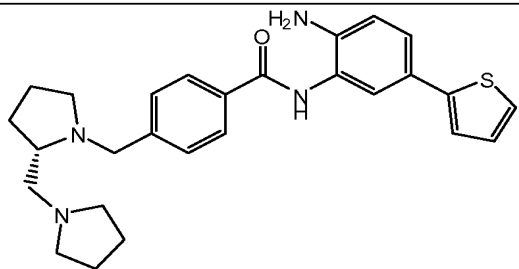
**p21<sup>WAF1/Cip1</sup> Assay.**

[1068] HCT116 cells were stably transfected with reporter plasmids encoding the p21 promoter-driven luciferase. Cells were treated with indicated concentration of HDAC inhibitors for 16 hours before cells were harvested and luciferase activity analyzed. The effective concentration (EC) of MS-275 was designated as 1  $\mu$ M. The ability of HDAC inhibitor was compared with that of MS-275 (T. Suzuki, et. al J. Med. Chem., 1999, 3001-3003). Lower EC of a given compound indicates that this compound is more potent than MS-275 to induce p21 expression.

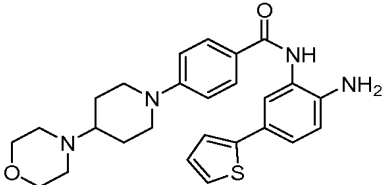
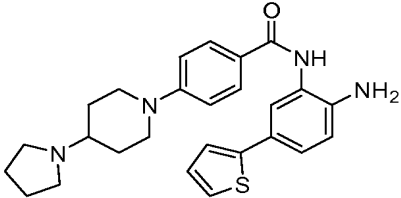
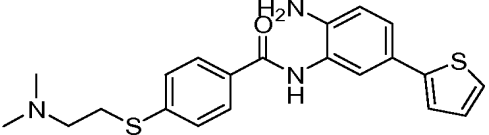
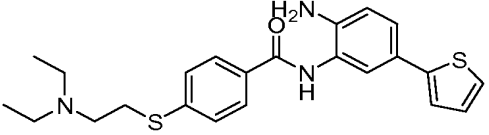
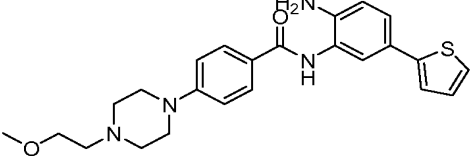
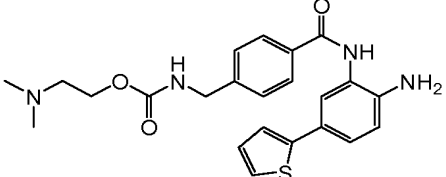
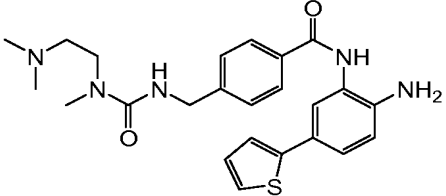
Table 21

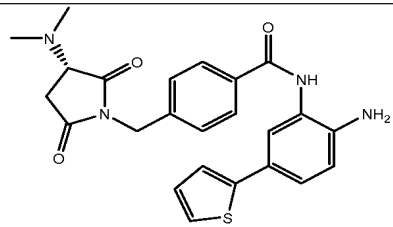
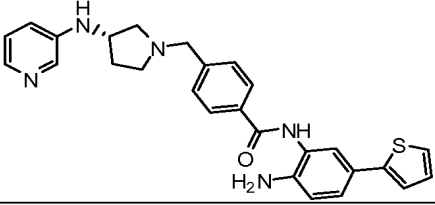
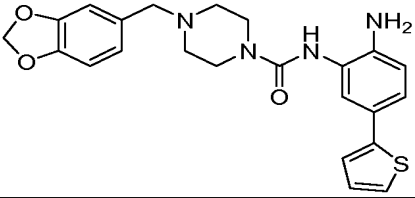
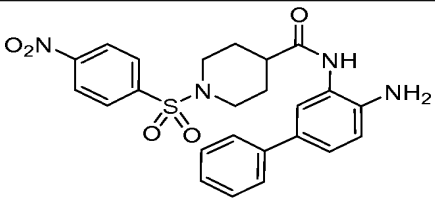
Ex	Cpd	Structure	HDAC -1 ( $\mu$ M)	MTT HCT1 16 ( $\mu$ M)	Sch eme	Log D (pH 7.4)
1a	9		a	a	1	2.11
1b	10		a	a	1	3.10
1c	11		a	a	1	3.03
1d	12		a	b	1	3.86
1e	13		a	a	1	2.22

Ex	Cpd	Structure	HDAC -1 ( $\mu$ M)	MTT HCT1 16 ( $\mu$ M)	Sch eme	Log D (pH 7.4)
1f	14		a	a	1	3.20
1g	15		a	a	1	2.15
1h	16		a	a	1	3.30
1j	18		a	a	1	1.64
6b	77		a	a	6	2.59
6c	78		a	a	6	2.29
6d	79		a	a	6	3.19

Ex	Cpd	Structure	HDAC -1 ( $\mu$ M)	MTT HCT1 16 ( $\mu$ M)	Sch eme	Log D (pH 7.4)
6e	80		a	a	6	1.54
6f	81		a	a	6	2.11
6g	82		a	a	6	2.60
6h	83		a	b	6	2.60
6i	84		a	a	6	2.15
6j	85		a	a	6	3.32
6k	86		a	a	6	0.86

Ex	Cpd	Structure	HDAC -1 ( $\mu$ M)	MTT HCT1 16 ( $\mu$ M)	Sch eme	Log D (pH 7.4)
6l	87		a	a	6	2.15
6n	89		a	a	6	3.38
6o	90		a	a	6	3.15
6p	91		a	a	6	4.01
8a	101		a	a	8	1.94
8b	102		a	a	8	1.52
8c	103		a	a	8	2.68

Ex	Cpd	Structure	HDAC -1 ( $\mu$ M)	MTT HCT1 16 ( $\mu$ M)	Sch eme	Log D (pH 7.4)
8d	104		a	a	8	2.51
8e	105		a	a	8	1.60
8f	106		a	b	8	2.85
8g	107		a		8	2.58
8h	108		a	a	8	1.78
25a	221		a	a	25	1.85
25 b	222		a	a	25	1.05

Ex	Cpd	Structure	HDAC -1 ( $\mu$ M)	MTT HCT1 16 ( $\mu$ M)	Sch eme	Log D (pH 7.4)
27a	242		a	b	27	1.81
28a	249		a	a	28	3.27
35	316		a		36	2.32
36	320		a		37	3.21

[1069] Unless specified otherwise, in all the tables in this specification,  $a < 1 \mu\text{M}$ ;  $1 \mu\text{M} \leq b < 5 \mu\text{M}$ .

Table 22

Cpd number	HDAC IC <sub>50</sub>
441	D
284	A
61	B
147	C
148	C
173	C
283	A
62	B
150	C
161	B

Cpd number	HDAC IC <sub>50</sub>
65	B
174	B
56	B
57	C
149	D
132	A
172	D
140	C
184	B
19	B

Cpd number	HDAC IC <sub>50</sub>
19	B
19	A
19	A
171	B
193	D
194	D
170	A
43	C
44	C
42	C

Cpd number	HDAC IC <sub>50</sub>
47	C
12	B
64	B
64	B
17	B
17	B
9	A
9	A
101	B
101	B

Cpd number	HDAC IC50
49	<b>B</b>
49	<b>A</b>
49	<b>B</b>
201	<b>D</b>
127	<b>B</b>
209	<b>C</b>
210	<b>C</b>
14	<b>C</b>
14	<b>B</b>
15	<b>B</b>
13	<b>B</b>
13	<b>B</b>
16	<b>B</b>
124	<b>B</b>
125	<b>C</b>
11	<b>B</b>
11	<b>B</b>
23	<b>C</b>
66	<b>B</b>
25	<b>C</b>
24	<b>B</b>
108	<b>B</b>
108	<b>A</b>
106	<b>C</b>
21	<b>B</b>
20	<b>A</b>
103	<b>B</b>
105	<b>A</b>
105	<b>A</b>
22	<b>B</b>
10	<b>B</b>
102	<b>B</b>
104	<b>B</b>
104	<b>A</b>
50	<b>B</b>
50	<b>B</b>
63	<b>C</b>
107	<b>B</b>
205	<b>C</b>
76	<b>B</b>
221	<b>B</b>

Cpd number	HDAC IC50
126	<b>B</b>
126	<b>B</b>
77	<b>B</b>
18	<b>B</b>
166	<b>B</b>
78	<b>B</b>
78	<b>D</b>
79	<b>B</b>
80	<b>B</b>
488	<b>C</b>
488	<b>D</b>
299	<b>B</b>
300	<b>C</b>
521	<b>A</b>
81	<b>A</b>
81	<b>B</b>
82	<b>B</b>
222	<b>A</b>
26	<b>B</b>
84	<b>B</b>
83	<b>B</b>
27	<b>B</b>
85	<b>A</b>
85	<b>B</b>
85	<b>A</b>
86	<b>B</b>
86	<b>A</b>
67	<b>C</b>
87	<b>A</b>
87	<b>A</b>
436	<b>A</b>
436	<b>B</b>
436	<b>B</b>
436	<b>A</b>
474	<b>B</b>
232	<b>B</b>
230	<b>A</b>
176	<b>A</b>
177	<b>A</b>
179	<b>A</b>
242	<b>A</b>

Cpd number	HDAC IC50
28	<b>C</b>
88	<b>A</b>
89	<b>B</b>
90	<b>A</b>
29	<b>C</b>
249	<b>A</b>
249	<b>A</b>
231	<b>A</b>
68	<b>C</b>
30	<b>D</b>
31	<b>C</b>
33	<b>D</b>
216	<b>B</b>
32	<b>D</b>
69	<b>C</b>
51	<b>A</b>
51	<b>B</b>
91	<b>B</b>
92	<b>A</b>
226	<b>B</b>
227	<b>B</b>
178	<b>A</b>
265	<b>D</b>
233	<b>B</b>
175	<b>A</b>
271	<b>A</b>
271	<b>A</b>
235	<b>A</b>
234	<b>A</b>
260	<b>D</b>
261	<b>D</b>
262	<b>D</b>
70	<b>C</b>
71	<b>C</b>
285	<b>A</b>
286	<b>C</b>
287	<b>C</b>
301	<b>B</b>
302	<b>A</b>
510	<b>D</b>
253	<b>B</b>

Cpd number	HDAC IC50
58	<b>C</b>
109	<b>A</b>
288	<b>B</b>
288	<b>B</b>
288	<b>D</b>
303	<b>C</b>
289	<b>B</b>
289	<b>C</b>
72	<b>B</b>
305	<b>C</b>
290	<b>C</b>
308	<b>C</b>
304	<b>C</b>
110	<b>A</b>
338	<b>A</b>
307	<b>D</b>
291	<b>C</b>
339	<b>A</b>
340	<b>A</b>
340	<b>B</b>
341	<b>A</b>
278	<b>C</b>
96	<b>B</b>
96	<b>C</b>
306	<b>D</b>
292	<b>A</b>
292	<b>B</b>
279	<b>B</b>
380	<b>C</b>
431	<b>A</b>
381	<b>C</b>
293	<b>B</b>
293	<b>D</b>
475	<b>C</b>
379	<b>B</b>
518	<b>B</b>
327	<b>B</b>
327	<b>B</b>
327	<b>B</b>
327	<b>A</b>
327	<b>A</b>



Cpd number	HDAC IC50
327	<b>B</b>
327	<b>A</b>
327	<b>A</b>
327	<b>B</b>
327	<b>A</b>
327	<b>B</b>
327	<b>A</b>
327	<b>A</b>
309	<b>B</b>
294	<b>A</b>
520	<b>C</b>
295	<b>B</b>
296	<b>A</b>
310	<b>A</b>
320	<b>C</b>
519	<b>A</b>
519	<b>B</b>
316	<b>C</b>
328	<b>B</b>
328	<b>A</b>
372	<b>A</b>
389	<b>B</b>
342	<b>B</b>
343	<b>B</b>
477	<b>B</b>
337	<b>B</b>
345	<b>B</b>
346	<b>C</b>
517	<b>B</b>
348	<b>B</b>
350	<b>A</b>
351	<b>C</b>
352	<b>B</b>
353	<b>D</b>
354	<b>D</b>
516	<b>A</b>
342	<b>B</b>
355	<b>B</b>
356	<b>C</b>
357	<b>A</b>
341	<b>A</b>

Cpd number	HDAC IC50
347	<b>B</b>
515	<b>C</b>
506	<b>C</b>
427	<b>C</b>
514	<b>C</b>
507	<b>B</b>
358	<b>B</b>
359	<b>C</b>
360	<b>C</b>
361	<b>C</b>
362	<b>D</b>
349	<b>C</b>
508	<b>B</b>
363	<b>B</b>
364	<b>C</b>
513	<b>B</b>
365	<b>C</b>
366	<b>C</b>
367	<b>C</b>
373	<b>C</b>
368	<b>D</b>
522	<b>C</b>
369	<b>D</b>
523	<b>D</b>
512	<b>B</b>
422	<b>B</b>
370	<b>B</b>
371	<b>B</b>
447	<b>D</b>
487	<b>A</b>
487	<b>A</b>
487	<b>B</b>
481	<b>B</b>
481	<b>A</b>
481	<b>B</b>
537	<b>D</b>
509	<b>C</b>
330	<b>A</b>
330	<b>B</b>
330	<b>B</b>
330	<b>A</b>

Cpd number	HDAC IC50
330	<b>D</b>
503	<b>C</b>
504	<b>C</b>
505	<b>D</b>
412	<b>B</b>
374	<b>C</b>
375	<b>B</b>
376	<b>C</b>
501	<b>D</b>
336	<b>B</b>
502	<b>C</b>
377	<b>B</b>
378	<b>B</b>
466	<b>C</b>
500	<b>D</b>
511	<b>A</b>
467	<b>D</b>
468	<b>B</b>
468	<b>A</b>
497	<b>A</b>
496	<b>B</b>
329	<b>A</b>
388	<b>C</b>
387	<b>A</b>
385	<b>C</b>
469	<b>B</b>
392	<b>C</b>
383	<b>C</b>
486	<b>A</b>
382	<b>A</b>
386	<b>C</b>
495	<b>C</b>
493	<b>B</b>
384	<b>C</b>
470	<b>C</b>
398	<b>B</b>
499	<b>C</b>
530	<b>C</b>
531	<b>C</b>
480	<b>B</b>
492	<b>B</b>

Cpd number	HDAC IC50
471	<b>C</b>
472	<b>B</b>
529	<b>B</b>
529	<b>A</b>
485	<b>B</b>
485	<b>A</b>
484	<b>B</b>
479	<b>C</b>
479	<b>A</b>
524	<b>C</b>
525	<b>A</b>
491	<b>A</b>
498	<b>A</b>
483	<b>A</b>
528	<b>B</b>
527	<b>B</b>
526	<b>B</b>
494	<b>C</b>
482	<b>B</b>
406	<b>B</b>
490	<b>A</b>
489	<b>B</b>
408	<b>A</b>
478	<b>B</b>
476	<b>B</b>
464	<b>C</b>
465	<b>B</b>
541	<b>B</b>
539	<b>D</b>
540	<b>A</b>
552	<b>B</b>
551	<b>B</b>
444	<b>B</b>
532	<b>A</b>
533	<b>C</b>
460	<b>B</b>
535	<b>A</b>
536	<b>A</b>
538	<b>B</b>
416	<b>A</b>
473	<b>B</b>

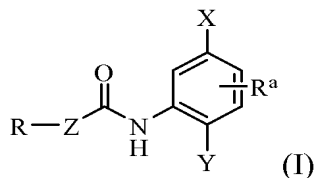
Cpd number	HDAC IC50
542	<b>A</b>
491	<b>A</b>
463	<b>C</b>
544	<b>C</b>
563	<b>A</b>
553	<b>A</b>
576	<b>A</b>
577	<b>A</b>
563	<b>C</b>
564	<b>C</b>
565	<b>C</b>
554	<b>C</b>
578	<b>B</b>
579	<b>A</b>
566	<b>A</b>
580	<b>A</b>
555	<b>B</b>
556	<b>B</b>
573	<b>C</b>
574	<b>B</b>
567	<b>D</b>
568	<b>D</b>
581	<b>C</b>
557	<b>A</b>
560	<b>A</b>
575	<b>B</b>
582	<b>B</b>
569	<b>A</b>
583	<b>B</b>
584	<b>B</b>
558	<b>A</b>
570	<b>A</b>
559	<b>C</b>
561	<b>C</b>
571	<b>C</b>
572	<b>C</b>

[1070] Unless specified otherwise, in all the tables in this specification,  $0.001 \leq A \leq 0.025 \mu\text{M}$ ,  $0.025 < B \leq 0.100 \mu\text{M}$ ,  $0.100 < C \leq 1 \mu\text{M}$ ;  $1 < D \leq 10 \mu\text{M}$  for HDAC1 and/or HDAC2;

[1071] Compounds of the invention on average possess increased bioavailability, increased solubility and/or lower Log D values than previously disclosed compounds, such as those of WO 05/030705. Consequently these new chemical entities are more soluble, less protein bound, and, ultimately, are expected to possess better pharmacological properties.

We claim:

1. A compound of formula I:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is phenyl, thienyl, pyridyl, or pyrimidyl, each of which is optionally substituted with one to three substituents independently selected from halo, -CN, -CH=N(OH), hydroxy, C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl, -O-C<sub>1</sub>-C<sub>4</sub>alkyl, -(CH<sub>2</sub>)<sub>0-3</sub>-N(R<sup>3</sup>)(R<sup>4</sup>), methoxy, or mono-, di-, or tri- halo substituted alkyl, or, when there are two optional substituents bonded to adjacent atoms of the phenyl, thienyl, or pyridyl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heterocycle having 1, 2, or 3 annular heteroatoms, which cycloalkyl or heterocycle is optionally substituted with oxo, alkyl and -C(O)-O-alkyl-heteroaryl;

Y is -NH<sub>2</sub> or OH;

R<sup>a</sup> is H or halo (preferably F);

Z is selected from the group consisting of a bond, phenyl, furyl, benzofuryl, pyridyl, -C<sub>1</sub>-C<sub>3</sub>alkyl-phenyl, -phenyl-C<sub>1</sub>-C<sub>3</sub>alkyl-heterocyclyl, -phenyl-alkenyl-, -phenyl-alkyl-, heterocyclyl and cycloalkyl, each of which is optionally substituted with C<sub>1</sub>-C<sub>3</sub>alkyl, -OMe or halo;

R is selected from the group consisting of H, -(CH<sub>2</sub>)<sub>0-3</sub>-N(R<sup>3</sup>)(R<sup>4</sup>), -(CH<sub>2</sub>)-C(O)-N(R<sup>3</sup>)(R<sup>4</sup>), -(CH<sub>2</sub>)<sub>0-2</sub>-C(O)-O-(CH<sub>2</sub>)<sub>2-3</sub>-N(R<sup>3</sup>)(R<sup>4</sup>), -(CH<sub>2</sub>)<sub>0-2</sub>-C(O)O-(CH<sub>2</sub>)<sub>0-3</sub>-heteroaryl, -(CH<sub>2</sub>)<sub>0-2</sub>-C(O)-O-(CH<sub>2</sub>)<sub>0-3</sub>-aryl, -SO<sub>2</sub>-(CH<sub>2</sub>)<sub>0-3</sub>-aryl, -SO<sub>2</sub>-N(R<sup>3</sup>)(R<sup>4</sup>), -SO<sub>2</sub>-(CH<sub>2</sub>)<sub>0-3</sub>-heteroaryl, -SO<sub>2</sub>-(CH<sub>2</sub>)<sub>0-3</sub>-heterocyclyl, indole, cycloocta-incole, -(CH<sub>2</sub>)<sub>2-3</sub>-heterocyclyl, -(CH<sub>2</sub>)<sub>0-3</sub>-aryl, -(CH<sub>2</sub>)<sub>0-3</sub>-heteroaryl, -(CH<sub>2</sub>)<sub>1-3</sub>-O-C(O)-C<sub>1-6</sub>alkyl (wherein the alkyl is optionally substituted with a moiety selected from the group consisting of

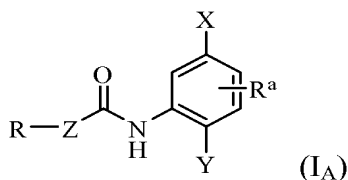
$-N(R^{30})(R^{31})$ ,  $-(CR^{32}R^{33})_s-N(R^{30})(R^{31})$ ,  $-Y^{31}-X^{30}$ , and  $-O-(CH_2)_{2-3}-N(R^3)(R^4)$ , and wherein the aryl, heteroaryl, heterocyclyl are each optionally substituted; or  
 $-Z-R$  is selected from the group consisting  $-C_1-C_8$ alkyl, -phenyl-heterocyclyl, -phenyl-dibenzo-oxazepine, -benzofuryl-heterocyclyl, -benzofuryl- $O-(CH_2)_{2-3}$ -heterocyclyl, -benzothieryl- $O-(CH_2)_{2-3}$ -heterocyclyl, or -benzofuryl  $-O-(CH_2)_{2-3}-N(R^3)(R^4)$ , each of which is optionally substituted; and  $R^3$  and  $R^4$  are independently selected from the group consisting of H,  $-C_1-C_6$  alkyl,  $-C_2-C_3$  alkyl- $OR^5$ , aryl, heteroaryl, -heteroaryl-heteroaryl, -heteroaryl-aryl, -aryl-heteroaryl,  $-C(O)$ -aryl,  $-C_1-C_3$ -alkoxy- $C_1-C_3$ -alkyl,  $-C_2-C_3$ alkyl- $O-C_1-C_3$ alkyl,  $-C_2-C_3$ -alkyl- $NR^5R^6$ ,  $-CH_2-C(CH_3)_2-NR^5R^6$ , wherein aryl and heteroaryl are optionally substituted with one, two or three amino, methoxy, hydroxyl,  $-S-CH_2$ -heteroaryl,  $-NR_3S(O)_2-C_1-C_3$ alkyl, or  
 $R^3$  and  $R^4$ , together with the nitrogen to which they are both bonded, form a 4- or 6-membered heterocyclyl with 1 or 2 annular heteroatoms (including the nitrogen to which  $R^3$  and  $R^4$  are bonded), which heterocyclyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of H, hydroxy, oxo, amino,  $-N=C(NR^3R^4)_2$ , one, two or three  $C_1-C_6$  alkyl, aryl, heteroaryl,  $-C_1-C_6$  alkyl-aryl,  $-C_1-C_6$  alkyl-heteroaryl,  $-C_1-C_3$ -alkoxy- $C_1-C_3$ -alkyl,  $-C_0-C_3$ -alkyl- $SR^7$ ,  $-C_2-C_3$ -alkyl-OH,  $-C_2-C_3$ -alkyl- $O-C_1-C_4$ -alkyl,  $-C_5-C_6$ -cycloalkyl,  $-C_0-C_3$ -alkyl- $N(R^3)-C(O)-C_1-C_3$ alkyl,  $-C_0-C_3$ alkyl- $N(R^3)-C(O)$ -thiomethyl,  $-C_0-C_3$ -alkyl- $NR^3C(O)O-C_1-C_3$ alkyl aryl,  $-C_0-C_3$ -alkyl- $CF_3$ ,  $-C_0-C_3$ -alkyl- $NR^3C(O)O-C_1-C_3$ alkyl heteroaryl and  $-C_0-C_3$ -alkyl- $N(R^7)(R^8)$ , wherein said heterocyclyl is optionally fused to an aryl or heteroaryl---;  
 $R^5$ ,  $R^6$ ,  $R^7$ , and  $R^8$  are independently selected from -H,  $-C_0-C_3$ -alkyl-aryl,  $-C_0-C_3$ -alkyl-heteroaryl,  $-C_0-C_3$ -alkyl-heterocyclyl,  $-C_0-C_3$ -alkyl-cycloalkyl and  $C_1-C_6$ -alkyl;  
s is an integer from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6;  
 $R^{32}$  and  $R^{33}$  are each independently selected from the group consisting of hydrogen, halo, hydroxyl,  $-C_0-C_3$ alkyl-aryl,  $-C_0-C_3$ alkyl-heteroaryl,  $-C_0-C_3$ alkyl-heterocyclyl,  $-C_0-C_3$ alkyl-cycloalkyl and  $C_1-C_4$ alkyl;

$R^{30}$  and  $R^{31}$  are each independently selected from the group consisting of hydrogen, cyano, oxo, hydroxyl,  $-C_1-C_8$ alkyl,  $C_1-C_8$ heteroalkyl,  $C_1-C_8$ alkenyl, carboxamido,  $C_1-C_3$ alkyl-carboxamido-, carboxamido- $C_1-C_3$ alkyl-, amidino,  $C_2-C_8$ hydroxyalkyl-,  $C_1-C_3$ alkylaryl-, aryl- $C_1-C_3$ alkyl-,  $C_1-C_3$ alkylheteroaryl-, heteroaryl- $C_1-C_3$ alkyl-,  $C_1-C_3$ alkylheterocyclyl-, heterocyclyl- $C_1-C_3$ alkyl-,  $C_1-C_3$ alkylcycloalkyl-, cycloalkyl- $C_1-C_3$ alkyl-,  $C_2-C_8$ alkoxy,  $C_2-C_8$ alkoxy- $C_1-C_4$ alkyl-,  $C_1-C_8$ alkoxycarbonyl-, aryloxycarbonyl-, aryl- $C_1-C_3$ alkoxycarbonyl-, heteroaryloxycarbonyl-, heteroaryl- $C_1-C_3$ alkoxycarbonyl-,  $C_1-C_8$ acyl,  $C_0-C_8$ alkyl-carbonyl-, aryl- $C_0-C_8$ alkyl-carbonyl-, heteroaryl- $C_0-C_8$ alkyl-carbonyl-, cycloalkyl- $C_0-C_8$ alkyl-carbonyl-,  $C_0-C_8$ alkyl-NH-carbonyl-, aryl- $C_0-C_8$ alkyl-NH-carbonyl-, heteroaryl- $C_0-C_8$ alkyl-NH-carbonyl-, cycloalkyl- $C_0-C_8$ alkyl-NH-carbonyl-,  $C_0-C_8$ alkyl-O-carbonyl-, aryl- $C_0-C_8$ alkyl-O-carbonyl-, heteroaryl- $C_0-C_8$ alkyl-O-carbonyl-, cycloalkyl- $C_0-C_8$ alkyl-O-carbonyl-,  $C_1-C_8$ alkylsulfonyl-, arylalkylsulfonyl-, arylsulfonyl-, heteroarylalkylsulfonyl-, heteroarylsulfonyl-,  $C_1-C_8$ alkyl-NH-sulfonyl-, arylalkyl-NH-sulfonyl-, aryl-NH-sulfonyl-, heteroarylalkyl-NH-sulfonyl-, heteroaryl-NH-sulfonyl-, aroyl, aryl, cycloalkyl, heterocyclyl, heteroaryl, aryl- $C_1-C_3$ alkyl-, cycloalkyl- $C_1-C_3$ alkyl-, heterocyclyl- $C_1-C_3$ alkyl-, heteroaryl- $C_1-C_3$ alkyl- and a protecting group, wherein each of the foregoing is further optionally substituted with one more moieties selected from halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino and guanidino; or  $R^{30}$  and  $R^{31}$  taken together with the N to which they are attached form a heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents selected from the group consisting of halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino, a protecting group, and  $(X^{30}-Y^{31}-)$ , wherein said heterocyclyl may also be bridged (forming a bicyclic moiety with a methylene, ethylene or propylene bridge);  $X^{30}$  is selected from the group consisting of  $C_1-C_8$ alkyl-,  $C_2-C_8$ alkenyl-,  $C_2-C_8$ alkynyl-,  $C_0-C_3$ alkyl- $C_2-C_8$ alkenyl- $C_0-C_3$ alkyl-,  $C_0-C_3$ alkyl- $C_2-C_8$ alkynyl- $C_0-C_3$ alkyl-,  $C_0-C_3$ alkyl-O- $C_0-C_3$ alkyl-, HO- $C_0-C_3$ alkyl-,  $C_0-C_4$ alkyl-N( $R^{30}$ )- $C_0-C_3$ alkyl-, N( $R^{30}$ )( $R^{31}$ )- $C_0-C_3$ alkyl-, N( $R^{30}$ )( $R^{31}$ )- $C_0-C_3$ alkenyl-, N( $R^{30}$ )( $R^{31}$ )- $C_0-C_3$ alkynyl-,

$(N(R^{30})(R^{31}))_2-C=N-$ ,  $C_0-C_3alkyl-S(O)_{0-2}-C_0-C_3alkyl-$ ,  $CF_3-C_0-C_3alkyl-$ ,  $C_1-C_8heteroalkyl$ , aryl, cycloalkyl, heterocyclyl, heteroaryl, aryl- $C_1-C_3alkyl-$ , cycloalkyl- $C_1-C_3alkyl-$ , heterocyclyl- $C_1-C_3alkyl-$ , heteroaryl- $C_1-C_3alkyl-$  and  $N(R^{30})(R^{31})-heterocyclyl-C_1-C_3alkyl-$ , wherein the aryl, cycloalkyl, heteroaryl and heterocycl are optionally substituted with from 1 to 3 substituents from halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino and guanidino; and

$Y^{31}$  is selected from the group consisting of a direct bond,  $-O-$ ,  $-N(R^{30})-$ ,  $-C(O)-$ ,  $-O-C(O)-$ ,  $-C(O)-O-$ ,  $-N(R^{30})-C(O)-$ ,  $-C(O)-N(R^{30})-$ ,  $-N(R^{30})-C(S)-$ ,  $-C(S)-N(R^{30})-$ ,  $-N(R^{30})-C(O)-N(R^{31})-$ ,  $-N(R^{30})-C(NR^{30})-N(R^{31})-$ ,  $-N(R^{30})-C(NR^{31})-$ ,  $-C(NR^{31})-N(R^{30})$ ,  $-N(R^{30})-C(S)-N(R^{31})-$ ,  $-N(R^{30})-C(O)-O-$ ,  $-O-C(O)-N(R^{31})-$ ,  $-N(R^{30})-C(S)-O-$ ,  $-O-C(S)-N(R^{31})-$ ,  $-S(O)_{0-2}-$ ,  $-SO_2N(R^{31})-$ ,  $-N(R^{31})-SO_2-$  and  $-N(R^{30})-SO_2N(R^{31})-$ ; provided that  $Y^{31}$  and  $X^{30}$  are not linked to form  $-O-O-$  or  $-O-N-$ .

2. A compound of Formula I<sub>A</sub>



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

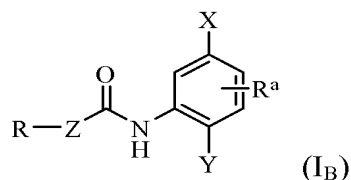
X is thienyl (preferably thien-2-yl);

Y is  $-NH_2$ ;

Z is pyridyl preferably pyrid-3-yl, furyl, heterocyclyl, or cycloalkyl;

R is  $-C(=NH)(N(R^3)(R^4))$ ,  $-C(NH_2)(=NOMe)$ ,  $-C(NH_2)(=NOH)$ ,  $-NR^3SO_2NR^3R^4$ ,  $-C\equiv C-C_1-C_3alkyl-NR^3R^4$ ,  $-C_0-C_3alkyl-aryl$  or  $-C_0-C_3alkyl-(5- or 6-membered heterocyclyl)$  optionally substituted with  $C_1-C_3-alkyl$  or  $-N(R^3)(R^4)$ , and  $R^a$ ,  $R^3$  and  $R^4$  are as defined in claim 1.

3. A compound of Formula I<sub>B</sub>:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is thienyl (preferably thienyl-2-yl), phenyl or pyridyl, each of which is optionally substituted with C<sub>1</sub>-C<sub>3</sub>alkyl or halo;

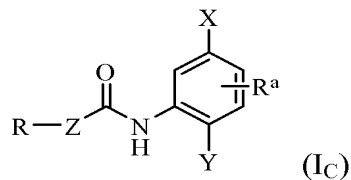
Y is -NH<sub>2</sub>;

Z is phenyl, pyridyl (preferably pyrid-2-yl), furyl, thienyl, heterocyclyl, or cycloalkyl;

R is an optionally substituted -C<sub>0</sub>-C<sub>3</sub>alkyl-aryl, -C(O)-aryl, -C<sub>0</sub>-C<sub>3</sub>alkyl-N(R<sup>3</sup>)-aryl, -C<sub>0</sub>-C<sub>3</sub>alkyl-(5- or 6- membered aryl or heteroaryl) (preferably optionally substituted with from 1 to 3 C<sub>1</sub>-C<sub>3</sub>-alkoxy); and

R<sup>a</sup>, R<sup>3</sup> are as defined in claim 1.

4. A compound of Formula I<sub>C</sub>:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is thienyl (preferably (thien-2-yl), phenyl, pyridyl, or pyridyl-N-oxide, wherein the thienyl may also be optionally substituted with halo or CN, and the phenyl and pyridyl moieties are optionally substituted with one or more halo;

Y is -NH<sub>2</sub>;

R<sup>a</sup> is H or F;

Z is aryl, 5- to 9- membered heterocyclyl, heteroaryl, or cycloalkyl, each of which is optionally substituted with one or two substituents selected from halo, oxo, CN, hydroxy, C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl, methoxy, or mono-, di-, or tri- halo substituted alkyl, or,

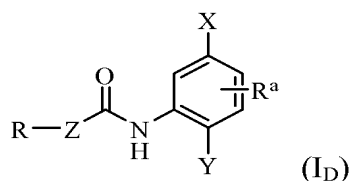


when there are two optional substituents bonded to adjacent atoms of the aryl, heteroaryl, or heterocyclyl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heterocycle having 1, 2, or 3 annular heteroatoms; and

R is H, halo, hydroxyl, C<sub>1</sub>-C<sub>3</sub>alkyl-OH, cyano, alkoxy, -C<sub>0</sub>-C<sub>3</sub>alkyl-N(R<sup>3</sup>)(R<sup>4</sup>), -C<sub>0</sub>-C<sub>3</sub>alkyl-N(R<sup>3</sup>)-C<sub>1</sub>-C<sub>3</sub>alkyl-CH(OH)-CH<sub>2</sub>OH, -C<sub>0</sub>-C<sub>2</sub>-alkyl-aryl or -C<sub>0</sub>-C<sub>2</sub>-alkyl-(5- or 6- membered heteroaryl or heterocyclyl), wherein the aryl, heteroaryl and heterocyclyl are optionally substituted with one to three independently selected moieties selected from the group consisting of methyl, halo, hydroxy, oxo-, -Y<sup>31</sup>-X<sup>30</sup>, or -(C R<sup>32</sup>R<sup>33</sup>)<sub>s</sub>-N(R<sup>30</sup>)(R<sup>31</sup>);

wherein R<sup>3</sup>, R<sup>4</sup>, R<sup>30</sup>, R<sup>31</sup>, R<sup>32</sup>, R<sup>33</sup>, s, Y<sup>31</sup> and X<sup>30</sup> are as defined in claim 1.

5. A compound of of Formula I<sub>D</sub>:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is thienyl (preferably thien-2-yl);

Y is -NH<sub>2</sub>;

R<sup>a</sup> is H or F;

Z is phenyl, heterocyclyl or cycloalkyl;

R is -(CH<sub>2</sub>)-N(R<sup>3</sup>)(R<sup>4</sup>);

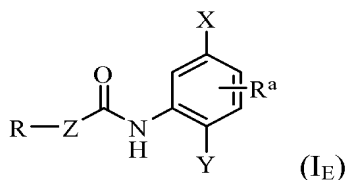
R<sup>3</sup> and R<sup>4</sup> are independently H, C<sub>1</sub>-C<sub>6</sub> alkyl, (5- or 6-membered heteroaryl)-C<sub>0</sub>-C<sub>2</sub>-alkyl-; or

R<sup>3</sup> and R<sup>4</sup>, together with the nitrogen to which they are both bonded, form a 5- or 6-membered heterocyclyl with 1 or 2 annular heteroatoms (including the nitrogen to which R<sup>3</sup> and R<sup>4</sup> are bonded), which heterocyclyl is optionally substituted with at least one (preferably one, two, or three) moieties independently selected from hydroxy, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -N(R<sup>5</sup>)(R<sup>6</sup>), C<sub>1</sub>-C<sub>6</sub> alkoxyC<sub>1</sub>-C<sub>6</sub>

alkyl,  $\text{-NR}^7\text{-C(O)-C}_1\text{-C}_2\text{-alkyl}$ ,  $\text{NR}^7\text{R}^8\text{-C}_0\text{-C}_3\text{-alkyl}$ , or (5- or 6-membered aryl, heterocyclyl or heteroaryl)- $\text{C}_0\text{-C}_2\text{-alkyl}$ ; and

$\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$ , and  $\text{R}^8$  are independently selected from -H and  $\text{C}_1\text{-C}_6\text{-alkyl}$ .

6. A compound of Formula I<sub>E</sub>:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is thienyl (preferably thien-2-yl), thiazolyl, pyridyl, pyrimidyl or phenyl optionally substituted with one, two or three halo, amino or methoxy;

Y is  $\text{-NH}_2$  or  $\text{-OH}$ ;

Z is phenyl, heterocyclyl or cycloalkyl; and

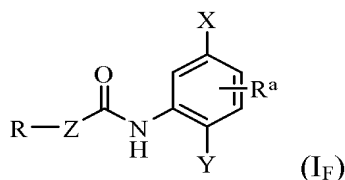
R is  $\text{N(R}^3\text{)(R}^4\text{)-C}_0\text{-C}_1\text{-alkyl-}$  or  $\text{N(R}^5\text{)(R}^6\text{)-C}_1\text{-C}_3\text{-alkyl-S-}$ ,  $\text{N(R}^{30}\text{)(R}^{31}\text{)-(C R}^{32}\text{R}^{33}\text{)}_s\text{-}$ , or  $\text{X}^{30}\text{-Y}^{31}\text{-}$ ; wherein

$\text{R}^3$  and  $\text{R}^4$  are independently -H,  $\text{-C}_1\text{-C}_6$  alkyl,  $\text{-C(O)-C}_0\text{-C}_3$  alkyl-aryl, aryl, -heteroaryl-aryl, -aryl-heteroaryl, aryl or heteroaryl and are optionally substituted with one, two or three halo,  $\text{CF}_3$ , amino or hydroxyl; or

$\text{R}^3$  and  $\text{R}^4$ , together with the nitrogen to which they are both bonded, form a 5- or 6-membered heterocyclyl with 1 or 2 annular heteroatoms (including the nitrogen to which  $\text{R}^3$  and  $\text{R}^4$  are bonded), which heterocyclyl is optionally substituted with  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_3\text{-alkoxy-C}_1\text{-C}_3\text{-alkyl-}$ ,  $\text{-N=C(NR}^3\text{R}^4\text{)}_2$ ,  $\text{-C(O)O-C}_0\text{-C}_3\text{alkyl-aryl}$ ,  $\text{-C(O)O-C}_0\text{-C}_3\text{alkyl-heteroaryl}$ , hydroxyl,  $\text{-N(R}^5\text{)(R}^6\text{)}$ ,  $\text{-C}_0\text{-C}_2\text{-alkyl-aryl}$ ,  $\text{-C}_0\text{-C}_2\text{-alkyl-(5- or 6-membered cycloalkyl, aryl, heterocyclyl or heteroaryl)}$ ,  $\text{-NH-aryl}$ , or  $\text{-NH-(5- or 6-membered cycloalkyl, heterocyclyl or heteroaryl)}$ ; and  $\text{R}^5$  and  $\text{R}^6$  are, independently, H,  $\text{-C}_0\text{-C}_3\text{alkyl-aryl}$ , heteroaryl- $\text{C}_0\text{-C}_3\text{alkyl-heteroaryl}$ ,  $\text{-SO}_2\text{-Me}$ ,  $\text{-C(O)-C}_1\text{-C}_4\text{alkyl}$  or  $\text{C}_1\text{-C}_3\text{-alkyl}$ ; and

wherein  $\text{R}^a$ ,  $\text{R}^{30}$ ,  $\text{R}^{31}$ ,  $\text{R}^{32}$ ,  $\text{R}^{33}$ , s,  $\text{Y}^{31}$  and  $\text{X}^{30}$  are as defined in claim 1.

7. A compound of Formula I<sub>F</sub>:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is thienyl (preferably thien-2-yl), phenyl, pyrimidyl or pyridyl;

Y is -NH<sub>2</sub>;

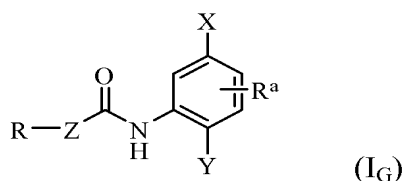
R<sup>a</sup> is H or F;

Z is pyrimid-5-yl, heterocyclyl, or cycloalkyl;

R is C<sub>1</sub>-C<sub>3</sub>-alkoxy or -N(R<sup>3</sup>)(R<sup>4</sup>); and

R<sup>3</sup> and R<sup>4</sup>, together with the nitrogen to which they are both bonded, form a 5- or 6-membered heterocyclyl, or bridged heterocyclyl, with 1 or 2 annular heteroatoms (including the nitrogen to which R<sup>3</sup> and R<sup>4</sup> are bonded), which heterocyclyl is optionally substituted with amino, hydroxyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>0</sub>-C<sub>2</sub>-alkyl-aryl or -C<sub>0</sub>-C<sub>2</sub>-alkyl-(5- or 6-membered cycloalkyl, heterocyclyl or heteroaryl), wherein the aryl is optionally substituted with one to three independently selected substituents selected from the group consisting of halo, methoxy, CF<sub>3</sub>, CN and alkyl.

8. A compound of Formula I<sub>G</sub>:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is aryl or a 5- or 6-membered heteroaryl optionally substituted with amino;

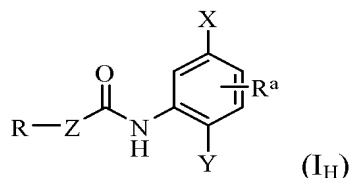
Y is -NH<sub>2</sub> or NHSO<sub>2</sub>NH<sub>2</sub>;

R<sup>a</sup> is H or F;

Z is phenyl, thienyl, heterocyclyl or cycloalkyl; and

R is C<sub>1</sub>-C<sub>3</sub>-alkoxy, aryl or a 5- or 6-membered heteroaryl.

9. A compound of Formula I<sub>H</sub>:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is aryl or 5- or 6-membered heteroaryl optionally substituted by one or two independently selected halo or CN;

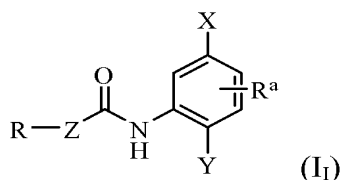
Y is -NH<sub>2</sub>;

R<sup>a</sup> is H or F;

Z is phenyl, heterocyclyl or cycloalkyl; and

R is a -C<sub>0</sub>-C<sub>1</sub>-alkyl-(aryl, heteroaryl or 5-10-membered heterocyclyl) optionally substituted by methyl or oxo.

10. A compound of Formula I<sub>I</sub>:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is thienyl;

Y is -NH<sub>2</sub>;

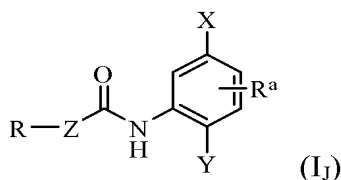
R<sup>a</sup> is H or F;

Z is phenyl, heterocyclyl or cycloalkyl, each of which is optionally substituted with -OH;

R is R<sup>8</sup>-C(O)-C<sub>0</sub>-C<sub>3</sub>-alkyl- or Ac-NH-; and

R<sup>8</sup> is -OH, HO-NH-, or CH<sub>3</sub>-O-.

11. A compound of Formula I<sub>J</sub>:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is cyclopentenyl, optionally substituted with oxo or hydroxy;

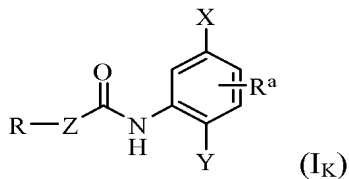
Y is -NH<sub>2</sub>;

R<sup>a</sup> is H or F;

Z is benzyl, -C<sub>0</sub>-C<sub>3</sub>alkyl-phenyl heterocyclyl or cycloalkyl; and

R is -C<sub>0</sub>-C<sub>3</sub>alkyl-morpholinyl.

12. A compound of Formula I<sub>K</sub>:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is aryl or 5- or 6-membered heteroaryl optionally substituted by one, two or three independently selected hydroxyl, -O-C<sub>1</sub>-C<sub>3</sub>alkyl, amino, -NR<sup>3</sup>R<sup>4</sup>, -CN, -CF<sub>3</sub>, -C<sub>1</sub>-C<sub>4</sub>alkyl, -S(O)<sub>0-2</sub>R<sup>5</sup>, -O-CF<sub>3</sub> or halo;

Y is -NH<sub>2</sub> or -OH;

R<sup>a</sup> is H or F;

Z is phenyl, heteroaryl, heterocyclyl, or cycloalkyl;

R is R<sup>9</sup>-(C<sub>0-6</sub>alkyl)N-C(O)-N(H)-(CH<sub>2</sub>)<sub>t</sub>,

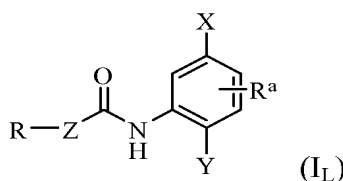
C<sub>0-6</sub>alkyl-S(O)<sub>2</sub>-N(H)-phenyl-C(O)-N(H)-(CH<sub>2</sub>)<sub>t</sub>, R<sup>9</sup>-O-C(O)-N(H)-(CH<sub>2</sub>)<sub>t</sub> or

R<sup>9</sup>-O-C(O)-(CH<sub>2</sub>)<sub>t</sub>-wherein t is 0-2; and

R<sup>9</sup> is R<sup>10</sup>-C<sub>0</sub>-C<sub>2</sub>-alkyl-,

wherein  $R^{10}$  is aryl, 5- or 6-membered heterocyclyl or heteroaryl or  $N(X^1)(X^2)-C_{0-3}alkyl$ -,  
 and  
 wherein  $X^1$  and  $X^2$  are independently H,  $C_1-C_4$ -alkyl or 5- or 6-membered heteroaryl,  
 or  
 $X^1$  and  $X^2$ , together with the N to which they are bonded form a 5- or 6-membered  
 heterocyclyl, which heterocyclyl and heteroaryl are optionally substituted with alkyl;  
 provided that when  $R^{10}$  is heterocyclyl attached through the N atoms, then  $R^9$  is  
 $R^{10}-C_2$ -alkyl-; and  
 wherein  $R^3$  and  $R^4$  are as defined in claim 1.

13. A compound of Formula  $I_L$ :



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or  
 complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers  
 thereof, wherein

X is aryl or 5- or 6-membered cycloalkyl, heterocyclyl, or heteroaryl optionally  
 substituted with hydroxy, oxo, or one or two halo;

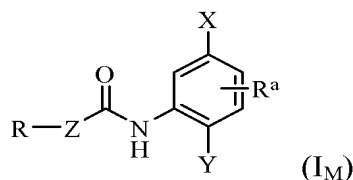
Y is -OH or -NH<sub>2</sub>;

Z is phenyl, pyridyl, benzofuryl, heterocyclyl, or cycloalkyl optionally substituted with  
 hydroxy, OMe or one or two halo, wherein when there are two optional substituents  
 bonded to adjacent atoms of the phenyl, or benzofuryl they, together with the atoms to  
 which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heteroalkyl  
 having 1, 2, or 3 annular heteroatoms; and

R is -OH, -OMe, -O- $C_0-C_3$ alkyl-heterocyclyl or -OAc; and

$R^a$  is as defined in claim 1.

14. A compound of Formula  $I_M$ :



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is thienyl;

Y is -NH<sub>2</sub>;

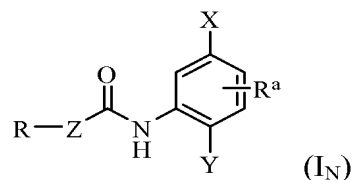
R<sup>a</sup> is H;

Z is phenyl, heterocyclyl or cycloalkyl;

R is R<sup>20</sup>-C(O)-(C<sub>2</sub>-C<sub>3</sub>-alkyl or C<sub>2</sub>-C<sub>3</sub>-alkenyl)-; and

R<sup>20</sup> is HO-, HO-NH-, or MeO-.

15. A compound of Formula I<sub>N</sub>:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is pyridyl;

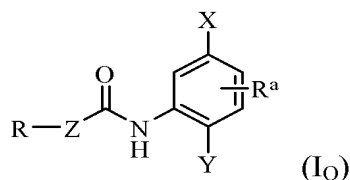
Y is -NH<sub>2</sub>;

R<sup>a</sup> is H or F;

Z is phenyl, heterocyclyl, cycloalkyl or heteroaryl, wherein phenyl, heterocyclyl, cycloalkyl or heteroaryl are optionally substituted with hydroxy, alkyloxy, or halo;  
and

R is -O-C<sub>0</sub>-C<sub>4</sub>-alkyl or -O-C<sub>2</sub>-C<sub>4</sub>-alkyl-heterocyclyl.

16. A compound of Formula I<sub>O</sub>:



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complexes thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is aryl, -aryl-heteroaryl, heterocyclyl, -heteroaryl-aryl or heteroaryl, wherein said aryl or heteroaryl is optionally substituted;

Y is  $\text{NH}_2$ ;

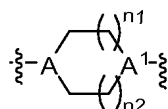
$\text{R}^a$  is H or halogen;

Z is benzofuryl, -benzofuryl-aryl, benzofuryl-heteroaryl, benzothiophene or phenyl, optionally substituted with one or more groups independently selected from  $\text{C}_1$ - $\text{C}_7$ alkyl, hydroxy,  $\text{C}_1$ - $\text{C}_7$ alkoxy, halo, CN and amino; and

R is H,  $-(\text{CR}^{32}\text{R}^{33})_s\text{-N}(\text{R}^{30})(\text{R}^{31})$ ,  $-\text{Y}^{31}\text{-X}^{30}$ , -O-heterocyclyl, -O- $\text{C}_2$ - $\text{C}_4$ alkyl- $\text{N}(\text{R}^{30})(\text{R}^{31})$ ,  $-(\text{CH}_2)_s\text{-N}(\text{R}^{30})(\text{R}^{31})$  or -O- $\text{C}_1$ - $\text{C}_3$ alkyl;

wherein  $\text{R}^{30}$ ,  $\text{R}^{31}$ ,  $\text{R}^{32}$ ,  $\text{R}^{33}$ , s,  $\text{Y}^{31}$  and  $\text{X}^{30}$  are as defined in claim 1.

17. The compound according to any of claims 1 to 16, wherein Z is



wherein A and  $\text{A}^1$  are independently  $\text{CR}^{11}$  or N,

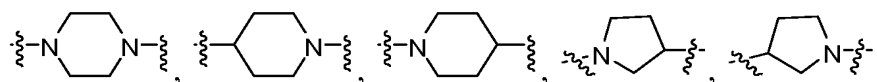
wherein  $\text{R}^{11}$  is -OH, alkyl, alkenyl, alkynyl or aryl, and

$n_1$  and  $n_2$  are each independently 0-3,

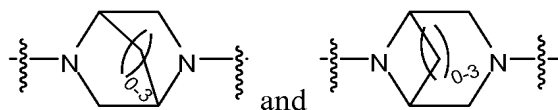
provided that when  $n_1$  and  $n_2$  are 0, then A and  $\text{A}^1$  are not both N.

18. The compound according to claim 17, wherein Z includes a 0 to 3 carbon bridge between non-adjacent carbon ring atoms.

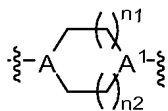
19. The compound according to claim 18, wherein Z is selected from the group consisting of







20. The compound according to any one of claims 1 to 16, wherein Z is



wherein A and A<sup>1</sup> are independently CR<sup>11</sup> or N,

wherein R<sup>11</sup> is -OH, alkyl, alkenyl, alkynyl or aryl,

n1 and n2 are each independently 0-3, and

R is R<sup>20</sup>-X<sup>50</sup>-,

wherein R<sup>20</sup> is aryl, -alkyl-aryl, heteroaryl, -alkyl-heteroaryl, cycloalkyl,

-alkyl-cycloalkyl, -alkyl-heterocyclyl or heterocyclyl, and

X<sup>50</sup> is C<sub>0</sub>-C<sub>3</sub>-alkyl-X<sup>51</sup>-C<sub>0</sub>-C<sub>3</sub>alkyl,

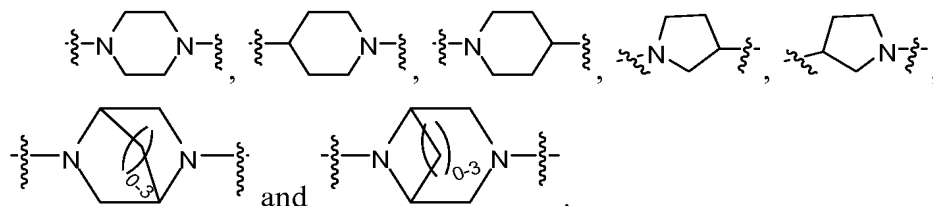
wherein X<sup>51</sup> selected from the group consisting of -SO<sub>2</sub>-, -NH-SO<sub>2</sub>-, -C(O)-, -NH-C(O)-,

-O-C(O)-, -C(S)-, -NH-C(S)-, -O-C(S)-, -NH-C(O)-NH-, -O-C(O)-NH- and

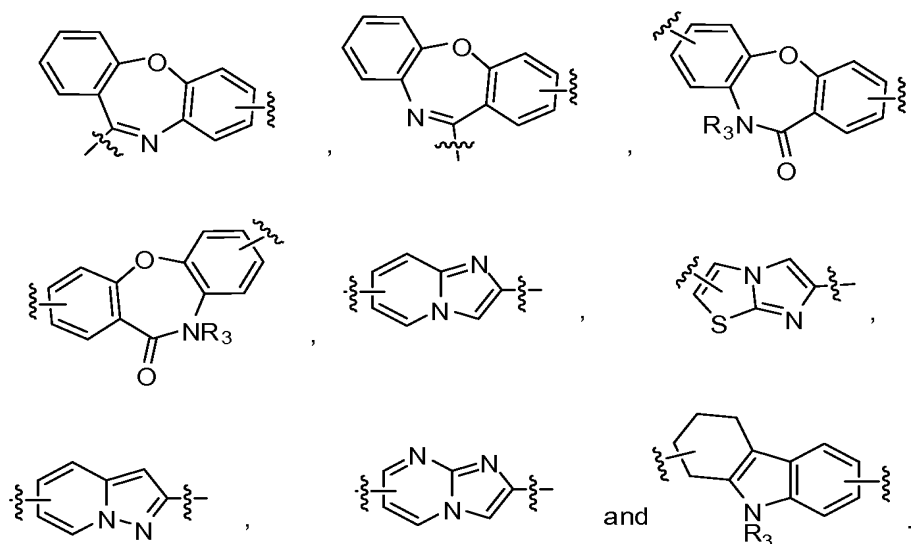
-NH-C(O)-O, provided that when n1 and n2 are 0, then A and A<sup>1</sup> are not both N.

21. The compound according to claim 20, wherein Z includes a 0 to 3 carbon bridge between non-adjacent carbon ring atoms.

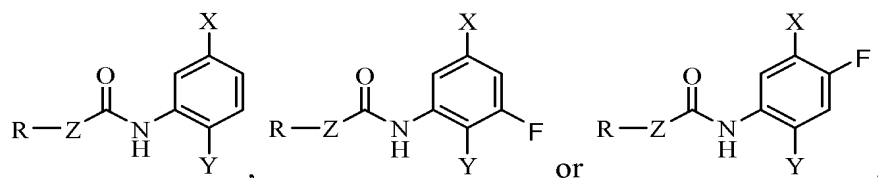
22. The compound according to claim 21, wherein Z is selected from the group consisting of



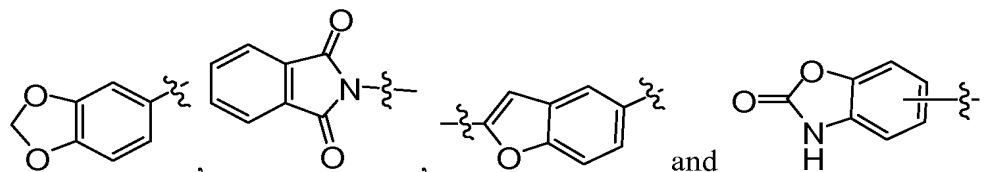
23. The compound according to any of claims 1 to 22, wherein Z is selected from the group consisting of



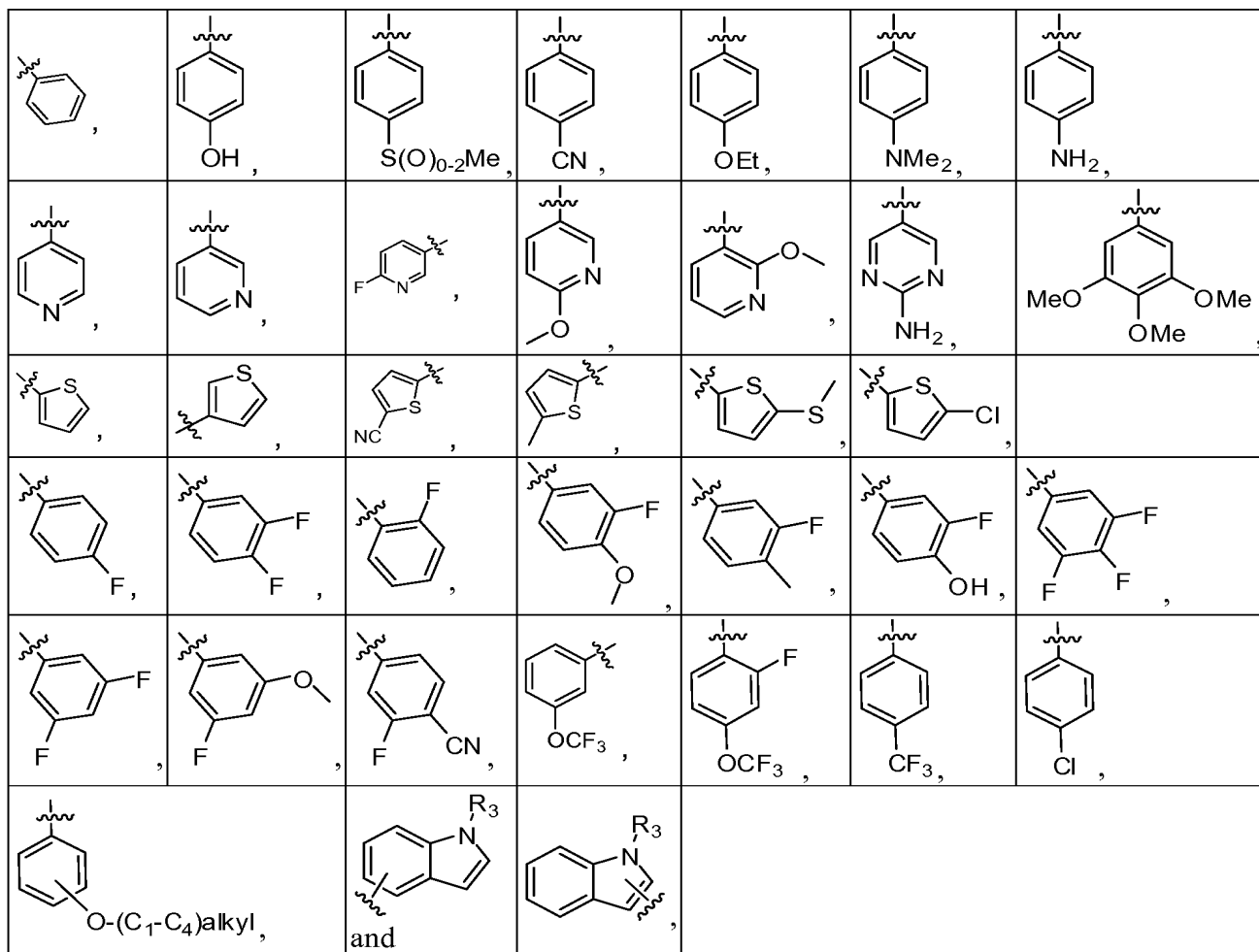
24. The compound according to claim 1, wherein  
 X is thienyl (preferably thien-2-yl), pyridyl (preferably pyrid-3-yl or 4-yl), or phenyl,  
 each optionally substituted as described for embodiment (I), and/or  
 R is morpholinyl, pyrrolidinyl, 2,5-diazabicyclo[2.2.1]heptane, azetidine, piperidinyl, or  
 piperazinyl (preferably piperazin-4-yl), each of which is optionally substituted with  
 hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl, C<sub>5</sub>-C<sub>6</sub>-cycloalkyl, or  
 NR<sup>7</sup>R<sup>8</sup>-C<sub>0</sub>-C<sub>3</sub>-alkyl.
25. The compound according to claim 1, wherein  
 -Z-R is -phenyl-heterocyclyl, optionally oxo substituted.
26. The compound according to claim 1, having as a generic structure



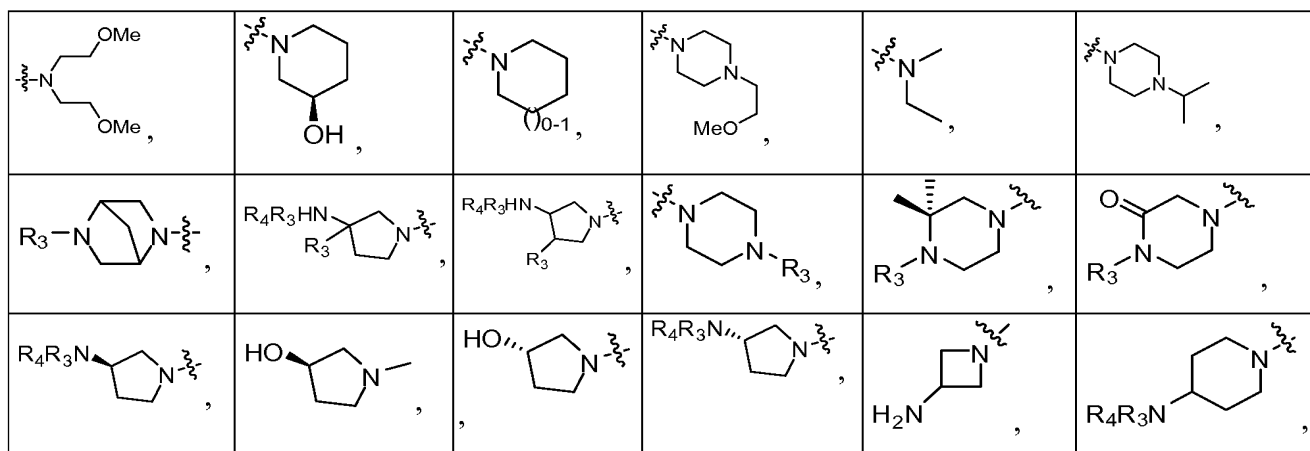
27. The compound according to claim 4, wherein, R is selected from the group consisting of

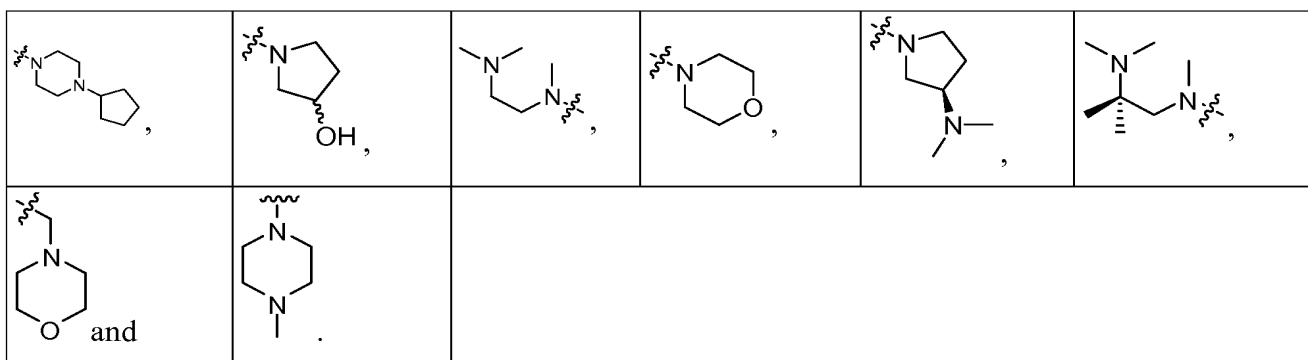


28. The compound according to any of claims 1 to 27, wherein X is selected from the group consisting of



and/or R is selected from the group consisting of



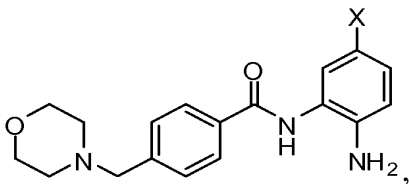


29. The compound according to claim 2, wherein  
 X is thien-2-yl;  
 Z is pyrid-3-yl; and  
 R is pyrrolidinyl (preferably pyrrolidin-1-yl), piperidinyl (preferably piperidin-1-yl), or piperazinyl (preferably piperazin-1-yl), each optionally substituted with C<sub>1</sub>-C<sub>3</sub>-alkyl, dialkylamino (preferably dimethylamino) or morpholino.
30. The compound according to claim 3, wherein  
 X is thien-2-yl;  
 Z is phenyl or pyridin-2-yl, and  
 R is thienyl (preferably thien-2-yl), 1*H*-pyrazolyl (preferably 1*H*-pyrazol-4-yl), or phenyl, optionally substituted with from 1 to 3 C<sub>1</sub>-C<sub>3</sub>-alkoxy (preferably methoxy).
31. The compound according to claim 4, wherein  
 X is thien-2-yl;  
 Z is phenyl, thienyl (preferably thien-2-yl), pyridyl (preferably pyrid-2-yl, -3-yl or -4-yl), furyl (preferably furan-2-yl), and  
 R is pyridyl (preferably pyridine-2-yl), pyrrolidinyl-C<sub>0</sub>-C<sub>2</sub>-alkyl (pyrrolidine-2-ylethyl), morpholino-C<sub>0</sub>-C<sub>1</sub>-alkyl, pyrrolyl (preferably pyrrol-1-yl), pyrazolyl (preferably pyrazol-1-yl), halo, or cyano.
32. The compound according to claim 5, wherein  
 X is thienyl-2-yl; and  
 R is -(CH<sub>2</sub>)-(piperidinyl, piperazinyl, or pyrrolidinyl), optionally substituted at least one (preferably one, two, or three) moieties independently selected from hydroxy, oxo, C<sub>1</sub>-C<sub>6</sub>

- alkyl, C<sub>1</sub>-C<sub>6</sub> alkyloxy, -N(R<sup>5</sup>)(R<sup>6</sup>), C<sub>1</sub>-C<sub>6</sub> alkyloxyC<sub>1</sub>-C<sub>6</sub> alkyl, -NR<sup>7</sup>-C(O)-C<sub>1</sub>-C<sub>2</sub>-alkyl, NR<sup>7</sup>R<sup>8</sup>-C<sub>0</sub>-C<sub>3</sub>-alkyl, and (5- or 6-membered aryl, heterocyclyl or heteroaryl)-C<sub>0</sub>-C<sub>2</sub>-alkyl.
33. The compound according to claim 6, wherein  
X is thienyl-2-yl optionally substituted with halo; and  
R is piperidinyl (preferably piperidin-1-yl), piperazinyl, or pyrrolidinyl, each optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl-, -N=C(NR<sup>3</sup>R<sup>4</sup>)<sub>2</sub>, -C(O)O-C<sub>0</sub>-C<sub>3</sub>alkyl-aryl, -C(O)O-C<sub>0</sub>-C<sub>3</sub>alkyl-heteroaryl, hydroxyl, -N(R<sup>5</sup>)(R<sup>6</sup>), -C<sub>0</sub>-C<sub>2</sub>-alkyl-aryl, -C<sub>0</sub>-C<sub>2</sub>-alkyl-(5- or 6-membered cycloalkyl, aryl, heterocyclyl or heteroaryl), -NH-aryl, or -NH-(5- or 6-membered cycloalkyl, heterocyclyl or heteroaryl).
34. The compound according to claim 7, wherein  
X is thiophen-2-yl;  
R is morpholino, or piperidinyl or piperazinyl each optionally substituted with amino, hydroxyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>0</sub>-C<sub>2</sub>-alkyl-aryl or -C<sub>0</sub>-C<sub>2</sub>-alkyl-(5- or 6-membered cycloalkyl, heterocyclyl or heteroaryl), wherein the aryl is optionally substituted with one to three independently selected substituents selected from the group consisting of halo, methoxy, CF<sub>3</sub>, CN and alkyl.
35. The compound according to claim 8, wherein  
X is thienyl (preferably thien-2-yl), phenyl, pyrrolyl (preferably pyrrol-2-yl), or 1H-pyrazolyl (preferably 1H-pyrazol-4-yl), each optionally substituted with amino;  
Y is amino or F; and  
R is methoxy or pyridyl (preferably pyridin-1-yl).
36. 37. The compound according to claim 9, wherein  
X is thienyl (preferably thien-2-yl), phenyl, pyridyl (preferably pyridine-2-yl), or furyl, each of which is optionally substituted with halo; and  
R is pyridyl (preferably pyridine-2-yl), piperidinyl optionally N-substituted with methyl, or morpholinomethyl.
37. The compound according to claim 12, wherein

- X is thienyl (preferably thien-2 or 3-yl), phenyl, pyridyl (preferably pyridine-2-yl) optionally substituted with 1 or 2 halo;  
 Y is -NH<sub>2</sub>; and  
 R<sup>10</sup> is -N(C<sub>1</sub>-C<sub>3</sub>-alkyl)(C<sub>1</sub>-C<sub>3</sub>-alkyl) (preferably dimethylamino).
38. The compound according to claim 13, wherein  
 X is thienyl (preferably thien-2-yl), pyridyl (preferably pyridine-2-yl), 3-oxo-cyclopent-1-yl, or phenyl, each of which is optionally substituted with 1 or two halo; and  
 Y is -NH<sub>2</sub> or -OH.
39. The compound according to claim 14, wherein  
 R is R<sup>20</sup>-C(O)-ethyl or R<sup>20</sup>-C(O)-ethenyl.
40. The compound according to claim 14, wherein R is selected from the group consisting of  
                     HO-C(O)-CH=CH-,  
                     HO-NH-C(O)-CH=CH-,  
                     MeO-C(O)-CH<sub>2</sub>-CH<sub>2</sub>- and  
                     HO-C(O)-CH<sub>2</sub>-CH<sub>2</sub>-.
41. The compound according to claim 16, wherein X is phenyl or pyridyl, each of which is optionally substituted.
42. The compound according to claim 16, wherein R is H, alkoxy, -O-(CH<sub>2</sub>)<sub>2-3</sub>-heterocycle or -O-(CH<sub>2</sub>)<sub>2-3</sub>-N(R<sup>3</sup>)(R<sup>4</sup>), wherein preferably the heterocycle moiety is morpholine or piperidine.
43. The compound according to claim 1, wherein X is optionally substituted with one, two or three substituents independently selected from the group consisting of halo, oxo, hydroxy, C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl, methoxy, HalCH<sub>2</sub>-O-, Hal<sub>2</sub>CH-O-, Hal<sub>3</sub>C-O- (preferably F<sub>3</sub>C-O-), NH<sub>2</sub>-, -N(C<sub>1</sub>-C<sub>3</sub>alkyl)<sub>2</sub>, -CN, -S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>4</sub>alkyl, -CF<sub>3</sub>, and mono-, di-, or tri-halo substituted alkyl, or, when there are two optional substituents bonded to adjacent atoms of the phenyl, thienyl, or pyridyl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heteroalkyl having 1, 2, or 3 annular heteroatoms.

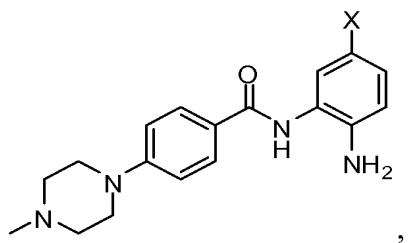
44. The compound according to claim 16, having the formula



wherein

X is aryl, -aryl-heteroaryl, heteroaryl-aryl, heterocyclyl or heteroaryl, wherein said aryl or heteroaryl is optionally substituted with one to three alkyl, halo, CN, alkyloxy, alkyl-OH, -OH, alkyl-NH<sub>2</sub>, -N(alkyl)<sub>2</sub>, alkyl-O-alkyl, -S(O)<sub>0-2</sub>alkyl, -C<sub>0</sub>-C<sub>3</sub>alkyl-NR<sub>3</sub>C(O)alkyl, -C(O)NR<sub>3</sub>alkyl, -alkyl-CN, CF<sub>3</sub>, -O-CF<sub>3</sub>, -C<sub>0</sub>-C<sub>3</sub>alkyl-C(O)OR<sub>3</sub>, -C<sub>0</sub>-C<sub>3</sub>alkyl-NR<sub>3</sub>C(O)Oalkyl, -C(O)Oalkyl, -S(O)<sub>2</sub>NHalkyl or -S(O)<sub>2</sub>NH<sub>2</sub>.

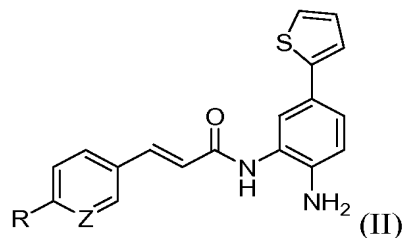
45. The compound according to claim 16, having the formula:



wherein

X is aryl, -aryl-heteroaryl, heterocyclyl, heteroaryl-aryl or heteroaryl, wherein said aryl or heteroaryl is optionally substituted with one to three alkyl, halo, CN, alkyloxy, alkyl-OH, -OH, alkyl-NH<sub>2</sub>, -N(alkyl)<sub>2</sub>, alkyl-O-alkyl, -S(O)<sub>0-2</sub>alkyl, -C<sub>0</sub>-C<sub>3</sub>alkyl-NR<sub>3</sub>C(O)alkyl, -C(O)NR<sub>3</sub>alkyl, -alkyl-CN, CF<sub>3</sub>, -O-CF<sub>3</sub>, -C<sub>0</sub>-C<sub>3</sub>alkyl-C(O)OR<sub>3</sub>, -C<sub>0</sub>-C<sub>3</sub>alkyl-NR<sub>3</sub>C(O)Oalkyl, -C(O)Oalkyl, -S(O)<sub>2</sub>NHalkyl or -S(O)<sub>2</sub>NH<sub>2</sub>.

46. A compound having Formula (II):



and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complex thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein


Z is N or CH;

R is  $-\text{CH}_2\text{OR}^3$ ,  $-\text{C}_0\text{-C}_3\text{alkyl-N(R}^3\text{)-C}_0\text{-C}_3\text{alkyl-heteroaryl}$ ,  $-\text{C}_0\text{-C}_3\text{alkyl-N(R}^3\text{)-C}_0\text{-C}_3\text{alkyl-aryl}$ ,  $-(\text{CH}_2)_m\text{-aryl}$ ,  $-(\text{CH}_2)_m\text{-heteroaryl}$  or (5- or 6-membered heteroaryl)- $(\text{CH}_2)_m$ -, wherein the aryl and heteroaryl rings are optionally substituted with 1, 2, or 3 methoxy;

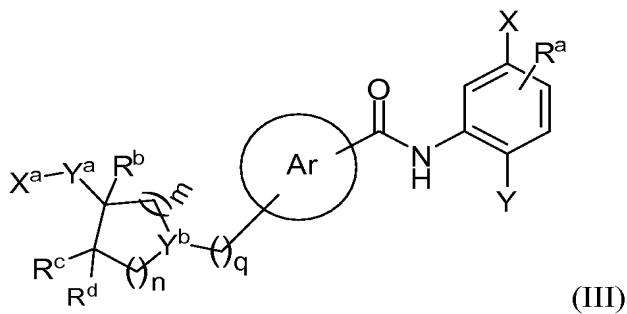
m is 0 or 1; and

$\text{R}^3$  is as defined in claim 1.

47. The compound according to claim 46, wherein R is pyridyl (preferably pyridine-2-yl), phenyl, or morpholino.

48. The compound according to claim 46, wherein the  moiety is optionally substituted with one, two or three substituents independently selected from the group consisting of halo, oxo, hydroxy,  $\text{C}_1\text{-C}_3\text{-hydrocarbonyl}$ , methoxy,  $\text{HalCH}_2\text{-O-}$ ,  $\text{Hal}_2\text{CH-O-}$ ,  $\text{Hal}_3\text{C-O-}$  (preferably  $\text{F}_3\text{C-O-}$ ),  $\text{NH}_2\text{-}$ ,  $-\text{N}(\text{C}_1\text{-C}_3\text{alkyl})_2$ ,  $-\text{CN}$ ,  $-\text{S(O)}_{0-2}\text{-C}_1\text{-C}_4\text{alkyl}$ ,  $-\text{CF}_3$ , and mono-, di-, or tri- halo substituted alkyl, or, when there are two optional substituents bonded to adjacent atoms of the phenyl, thienyl, or pyridyl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heteroalkyl having 1, 2, or 3 annular heteroatoms.

49. A compound having formula III





and N-oxides, hydrates, solvates, pharmaceutically acceptable salts, prodrugs or complex thereof and racemic and scalemic mixtures, diastereomers and enantiomers thereof, wherein

X is aryl, cycloalkyl, heteroaryl or heterocyclyl, each of which is optionally substituted;

Ar is aryl, heteroaryl, cycloalkyl or heterocyclyl, each of which is optionally substituted;

R<sup>a</sup> is H or halo;

R<sup>b</sup>, R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl or halo; or

R<sup>b</sup> and R<sup>c</sup> together with the atoms to which they are bonded, optionally form a 5- or 6-membered cycloalkyl or heteroalkyl having 1 or 2 annular heteroatoms; each of which is optionally substituted with from 1 to 3 substituents;

Y is -NH<sub>2</sub> or -OH;

Y<sup>b</sup> is -N- or -CH-;

Y<sup>a</sup> is direct bond, -O-, -N(R<sup>34</sup>)-, -C(O)-, -OC(O)-, -C(O)O-, -N(R<sup>34</sup>)-C(O)-, -C(O)-N(R<sup>34</sup>)-, -N(R<sup>34</sup>)-C(S)-, -C(S)-N(R<sup>34</sup>)-, -N(R<sup>34</sup>)-C(O)-N(R<sup>35</sup>)-, -N(R<sup>34</sup>)-C(NR<sup>34</sup>)-N(R<sup>35</sup>)-, -N(R<sup>34</sup>)-C(NR<sup>35</sup>)-, -C(NR<sup>35</sup>)-N(R<sup>34</sup>)-, -N(R<sup>34</sup>)-C(S)-N(R<sup>35</sup>)-, -N(R<sup>34</sup>)-C(O)-O-, -O-C(O)-N(R<sup>34</sup>)-, -N(R<sup>34</sup>)-C(S)O-, -O-C(S)-N(R<sup>35</sup>)-, -S(O)<sub>0-2</sub>-, -SO<sub>2</sub>N(R<sup>35</sup>)-, -N(R<sup>35</sup>)-SO<sub>2</sub>-, N(R<sup>34</sup>)-S(O)<sub>2</sub>N(R<sup>35</sup>)-, -O-C<sub>1</sub>-C<sub>3</sub>alkyl-, -N(R<sup>34</sup>)-C<sub>1</sub>-C<sub>3</sub>alkyl-, -C(O)-C<sub>1</sub>-C<sub>3</sub>alkyl- or -O-C(O)-C<sub>1</sub>-C<sub>3</sub>alkyl-;

X<sup>a</sup> is C<sub>1</sub>-C<sub>8</sub>alkyl-, C<sub>1</sub>-C<sub>8</sub>alkenyl-, C<sub>1</sub>-C<sub>8</sub>alkynyl-, C<sub>0</sub>-C<sub>3</sub>alkyl-C<sub>1</sub>-C<sub>8</sub>alkenyl-C<sub>0</sub>-C<sub>3</sub>alkyl-, C<sub>0</sub>-C<sub>3</sub>alkyl-C<sub>1</sub>-C<sub>8</sub>alkynyl-C<sub>0</sub>-C<sub>3</sub>alkyl-, C<sub>1</sub>-C<sub>3</sub>alkyl-O-C<sub>1</sub>-C<sub>3</sub>alkyl-, HO-C<sub>1</sub>-C<sub>3</sub>alkyl-, C<sub>1</sub>-C<sub>4</sub>alkyl-N(R<sup>34</sup>)-C<sub>0</sub>-C<sub>3</sub>alkyl-, N(R<sup>34</sup>)(R<sup>35</sup>)-C<sub>0</sub>-C<sub>3</sub>alkyl-, C<sub>1</sub>-C<sub>3</sub>alkyl-S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>3</sub>alkyl-, CF<sub>3</sub>-C<sub>0</sub>-C<sub>3</sub>alkyl-, CF<sub>2</sub>H-C<sub>0</sub>-C<sub>3</sub>alkyl-, C<sub>1</sub>-C<sub>8</sub>heteroalkyl-, aryl, cycloalkyl, heterocyclyl, heteroaryl, aryl-C<sub>1</sub>-C<sub>3</sub>alkyl-, cycloalkyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, heterocyclyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, heteroaryl-C<sub>1</sub>-C<sub>3</sub>alkyl-, aryl-C<sub>0</sub>-C<sub>2</sub>alkyl-heterocyclyl-C<sub>0</sub>-C<sub>2</sub>alkyl-, heteroaryl-C<sub>0</sub>-C<sub>2</sub>alkyl-heterocyclyl-C<sub>0</sub>-C<sub>2</sub>alkyl-, N(R<sup>34</sup>)(R<sup>35</sup>)-heterocyclyl-C<sub>0</sub>-C<sub>3</sub>alkyl-, heteroaryl-C<sub>0</sub>-C<sub>3</sub>alkyl-heterocyclyl- or C<sub>1</sub>-C<sub>4</sub>alkyl-CH(N(R<sup>34</sup>)(R<sup>35</sup>))-C(O)-N(R<sup>34</sup>)-aryl-, wherein the aryl, cycloalkyl, heteroaryl and heterocycyl are optionally substituted with from 1 to 3 independently selected substituents;

or

X<sup>a</sup>-Y<sup>a</sup>- is selected from the group consisting of H-, halo-, HO-, HS-, HC(O)-, HOC(O)-, C<sub>1</sub>-C<sub>4</sub>alkyl-, H<sub>2</sub>N-, (R<sup>34</sup>)(R<sup>35</sup>)N-, C<sub>1</sub>-C<sub>4</sub>alkyl-NH-, (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>-N-, HC(O)N(R<sup>34</sup>)-, (R<sup>34</sup>)(R<sup>35</sup>)N-S(O)<sub>2</sub>-N(R<sup>36</sup>)-, (R<sup>34</sup>)(R<sup>35</sup>)N-C(O)-, H<sub>2</sub>N-C(O)-, HC(S)N(R<sup>34</sup>)-, (R<sup>34</sup>)(R<sup>35</sup>)N-C(S)-, H<sub>2</sub>N-C(S)-, (R<sup>34</sup>)(R<sup>35</sup>)N-C(O)-O-, (R<sup>34</sup>)(R<sup>35</sup>)N-C(S)-O-, (R<sup>34</sup>)(R<sup>35</sup>)N-C(O)-N(R<sup>36</sup>)-, (C<sub>1</sub>-C<sub>3</sub>alkylN)<sub>2</sub>-C=N-, (R<sup>34</sup>)(R<sup>35</sup>)N-C(NR<sup>37</sup>)-N(R<sup>36</sup>)-, (R<sup>34</sup>)(R<sup>35</sup>)N-C(NR<sup>36</sup>)-, cycloalkyl-C<sub>0</sub>-C<sub>2</sub>alkyl-C(NR<sup>36</sup>)-, heterocyclyl-C<sub>0</sub>-C<sub>2</sub>alkyl-C(NR<sup>36</sup>)-, aryl-C<sub>0</sub>-C<sub>2</sub>alkyl-C(NR<sup>36</sup>)-, heteroaryl-C<sub>0</sub>-C<sub>2</sub>alkyl-C(NR<sup>36</sup>)-, C<sub>0</sub>-C<sub>3</sub>alkyl-C(NR<sup>36</sup>)-, C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-N(R<sup>36</sup>)-, CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-N(R<sup>36</sup>)-, CF<sub>3</sub>-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(R<sup>36</sup>)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-N(R<sup>36</sup>)-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-N(R<sup>36</sup>)-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-N(R<sup>36</sup>)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>2</sub>-N(R<sup>36</sup>)-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C(O)-NH-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-C<sub>1</sub>-C<sub>4</sub>alkyl-, C<sub>1</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-NH-C(O)-O-, C<sub>1</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-, C<sub>1</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-, Me-C(O)-O-, Me-C(O)-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(C<sub>1</sub>-C<sub>4</sub>alkyl)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(C<sub>1</sub>-C<sub>4</sub>alkyl)-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(C<sub>1</sub>-C<sub>4</sub>alkyl)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(O)-N(C<sub>1</sub>-C<sub>4</sub>alkyl)-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-,

cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-,  
 cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-,  
 aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-,  
 aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-,  
 aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-, heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-,  
 heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-,  
 heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-,  
 heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-, cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-,  
 heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-, aryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-NH-,  
 heteroaryl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-, heterocyclyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-,  
 cycloalkyl-C<sub>0</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>1</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-O-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-, HO-C<sub>1</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-,  
 HO-C<sub>1</sub>-C<sub>4</sub>alkyl-N(H)-, HO-C<sub>1</sub>-C<sub>4</sub>alkyl-N(R<sup>3</sup>)-, HO-C<sub>1</sub>-C<sub>4</sub>alkyl-O-,  
 HO-C<sub>1</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-, HO-C<sub>2</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-,  
 HO-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-, HO-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>1</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-,  
 C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)C(S)-N(H)-, C<sub>1</sub>-C<sub>4</sub>alkyl-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-,  
 HO-C<sub>2</sub>-C<sub>4</sub>alkyl-O-C(S)-N(H)-, HO-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-,  
 HO-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-, (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>1</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-,  
 (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>1</sub>-C<sub>4</sub>alkyl-C(O)-N(H)-, (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>1</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-,  
 (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>1</sub>-C<sub>4</sub>alkyl-C(O)-O-, (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-,  
 (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>2</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-,  
 (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(NH)-N(H)-,  
 (C<sub>0</sub>-C<sub>4</sub>alkyl)-O-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-, (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-O-C(O)-N(H)-,  
 (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-, (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-O-,  
 (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-S(O)<sub>0-2</sub>-, (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-N(H)-,  
 (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(O)-O-, (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>1</sub>-C<sub>4</sub>alkyl-C(S)-N(H)-,  
 (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-N(H)-,  
 (C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>N-C<sub>2</sub>-C<sub>4</sub>alkyl-N(H)-C(S)-O-,

$(C_1-C_4\text{alkyl})-O-C(O)C_1-C_8\text{alkyl}-C(O)-(H)-$ ,  $HO-C(O)C_1-C_8\text{alkyl}-C(O)-N(H)-$ ,  
 $HO-NH-C(O)C_1-C_8\text{alkyl}-C(O)-N(H)-$ ,  $CF_2H-C_0-C_4\text{alkyl}-C(O)-N(H)-$ ,  
 $CF_3-C_0-C_4\text{alkyl}-C(O)-N(H)-$ ,  $CF_3-C_0-C_4\text{alkyl}-N(H)-$ ,  $CF_3-C_0-C_4\text{alkyl}-N(R^{34})-$ ,  
 $CF_3-C_0-C_4\text{alkyl}-O-$ ,  $CF_3-C_0-C_4\text{alkyl}-S(O)_{0-2}-$ ,  $CF_3-C_0-C_4\text{alkyl}-O-C(O)-N(H)-$ ,  
 $CF_3-C_0-C_4\text{alkyl}-N(H)C(O)-N(H)-$ ,  $CF_3-C_0-C_4\text{alkyl}-N(H)-C(O)-O-$ ,  
 $CF_3-C_0-C_4\text{alkyl}-O-C(S)-N(H)-$ ,  $CF_3-C_0-C_4\text{alkyl}-N(H)-C(S)-N(H)-$ ,  
 $CF_3-C_0-C_4\text{alkyl}-N(H)-C(S)-O-$ ,  $CF_3-C_0-C_4\text{alkyl}-C(S)-N(H)-$ ,  $CF_2H-C_0-C_4\text{alkyl}-N(H)-$ ,  
 $CF_2H-C_0-C_4\text{alkyl}-O-$ ,  $CF_2H-C_0-C_4\text{alkyl}-S(O)_{0-2}-$ ,  $CF_2H-C_0-C_4\text{alkyl}-O-C(O)-N(H)-$ ,  
 $CF_2H-C_0-C_4\text{alkyl}-N(H)C(O)-N(H)-$ ,  $CF_2H-C_0-C_4\text{alkyl}-N(H)-C(O)-O-$ ,  
 $CF_2H-C_0-C_4\text{alkyl}-O-C(S)-N(H)-$ ,  $CF_2H-C_0-C_4\text{alkyl}-N(H)-C(S)-N(H)-$ ,  
 $CF_2H-C_0-C_4\text{alkyl}-N(H)-C(S)-O-$ ,  $CF_2H-C_0-C_4\text{alkyl}-C(S)-N(H)-$ ,  
 $(H)(R^{34})N-C_1-C_3\text{alkyl}-$ ,  $(H)(R^{34})N-C_1-C_3\text{alkyl}-$ ,  $HO-C_1-C_3\text{alkyl}-$ ,  
 $(H)(R^{34})N-S(O)_2-N(R^{35})-$ ,  $(H)(R^{35})N-S(O)_2-$ ,  $(H)(R^{34})N-C(S)-O-$ ,  $(H)(R^{34})N-C(O)-O-$ ,  
 $(H)(R^{34})N-C(S)-N(R^{35})-$ ,  $(H)(R^{34})N-C(NR^{35})-$ ,  $(H)(R^{34})N-C(NR^{34})-N(R^{38})-$ ,  
 $(H)(R^{34})N-C(O)-N(R^{35})-$ ,  $HO-C(O)-C_1-C_3\text{alkyl}-$ ,  $C_1-C_4\text{alkyl}-S(O)_2-NH-$  and  
 $((R^{34})(R^{35})N)_2-C=N-$ ;

m and n are independently 0, 1, 2 or 3;

q is 0, 1 or 2;

$R^{34}$ ,  $R^{35}$ ,  $R^{36}$  and  $R^{37}$  are each independently selected from the group consisting of  
 hydrogen, cyano, oxo, hydroxyl,  $-C_1-C_8\text{alkyl}$ ,  $C_1-C_8\text{heteroalkyl}$ ,  $C_1-C_8\text{alkenyl}$ ,  
 carboxamido,  $C_1-C_3\text{alkyl-carboxamido-}$ , carboxamido- $C_1-C_3\text{alkyl-}$ , amidino,  
 $C_2-C_8\text{hydroxyalkyl}$ ,  $C_1-C_3\text{alkylaryl-}$ , aryl- $C_1-C_3\text{alkyl-}$ ,  $C_1-C_3\text{alkylheteroaryl-}$ ,  
 heteroaryl- $C_1-C_3\text{alkyl-}$ ,  $C_1-C_3\text{alkylheterocyclyl-}$ , heterocyclyl- $C_1-C_3\text{alkyl-}$ ,  
 $C_1-C_3\text{alkylcycloalkyl-}$ , cycloalkyl- $C_1-C_3\text{alkyl-}$ ,  $C_2-C_8\text{alkoxy-}$ ,  
 $C_2-C_8\text{alkoxy-}C_1-C_4\text{alkyl-}$ ,  $C_1-C_8\text{alkoxycarbonyl-}$ , aryloxy- $C_1-C_3\text{alkyl-}$ ,  
 aryl- $C_1-C_3\text{alkoxycarbonyl-}$ , heteroaryloxy- $C_1-C_3\text{alkyl-}$ , heteroaryl- $C_1-C_3\text{alkoxycarbonyl-}$ ,  
 $C_1-C_8\text{acyl}$ ,  $C_0-C_8\text{alkyl-carbonyl-}$ , aryl- $C_0-C_8\text{alkyl-carbonyl-}$ ,  
 heteroaryl- $C_0-C_8\text{alkyl-carbonyl-}$ , cycloalkyl- $C_0-C_8\text{alkyl-carbonyl-}$ ,  
 $C_0-C_8\text{alkyl-N(H)-carbonyl-}$ , aryl- $C_0-C_8\text{alkyl-N(H)-carbonyl-}$ ,  
 heteroaryl- $C_0-C_8\text{alkyl-N(H)-carbonyl-}$ , cycloalkyl- $C_0-C_8\text{alkyl-N(H)-carbonyl-}$ ,  
 $C_0-C_8\text{alkyl-O-carbonyl-}$ , aryl- $C_0-C_8\text{alkyl-O-carbonyl-}$ ,

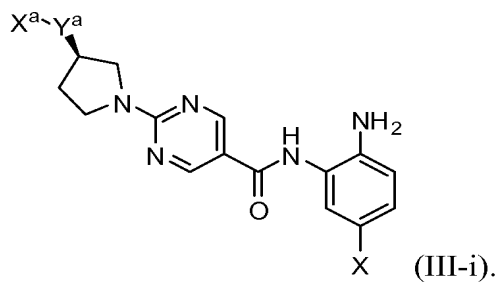
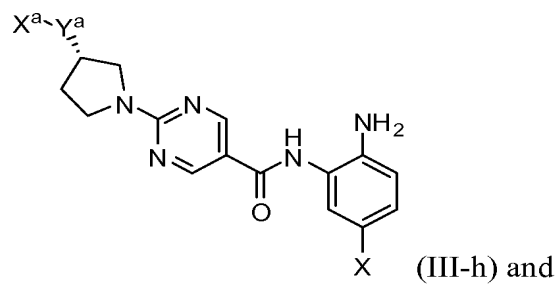
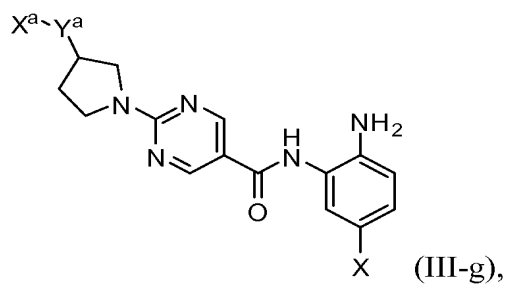
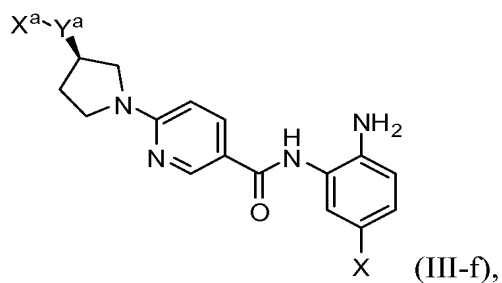
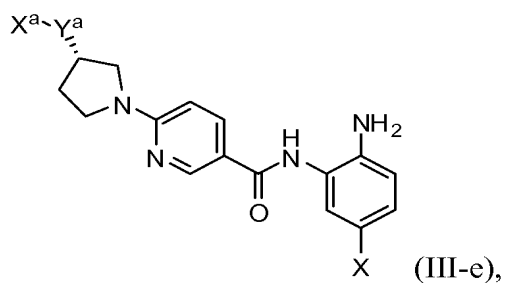
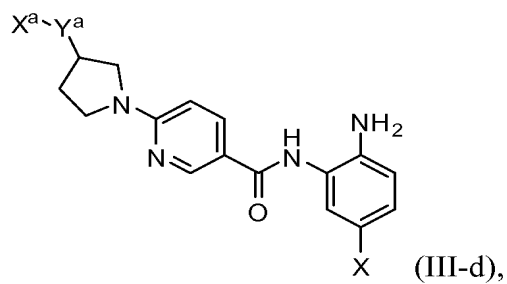
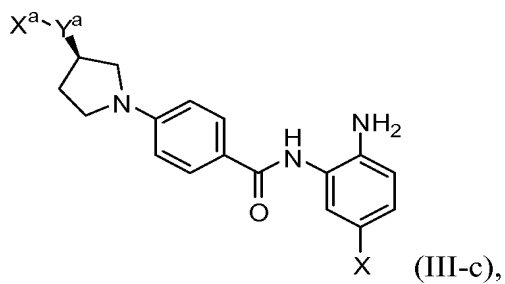
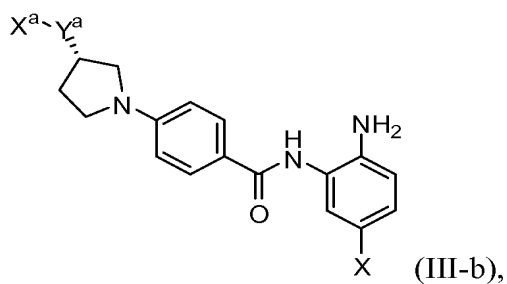
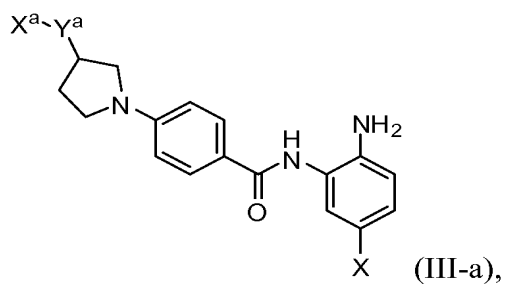
heteroaryl-C<sub>0</sub>-C<sub>8</sub>alkyl-O-carbonyl-, cycloalkyl-C<sub>0</sub>-C<sub>8</sub>alkyl-O-carbonyl-, C<sub>1</sub>-C<sub>8</sub> alkylsulfonyl-, arylalkylsulfonyl-, arylsulfonyl-, heteroarylalkylsulfonyl-, heteroarylsulfonyl-, C<sub>1</sub>-C<sub>8</sub>alkyl-N(H)-sulfonyl-, arylalkyl-N(H)-sulfonyl-, aryl-N(H)-sulfonyl-, heteroarylalkyl-N(H)-sulfonyl-, heteroaryl-N(H)-sulfonyl-, aroyl, aryl, cycloalkyl, heterocyclyl, heteroaryl, aryl-C<sub>1</sub>-C<sub>3</sub>alkyl-, cycloalkyl-C<sub>1</sub>-C<sub>3</sub>alkyl-, heterocyclyl-C<sub>1</sub>-C<sub>3</sub> alkyl-, heteroaryl-C<sub>1</sub>-C<sub>3</sub> alkyl-, and a protecting group, wherein each of the foregoing is further optionally substituted with one more moieties; or R<sup>34</sup> and R<sup>35</sup> taken together with the N to which they are attached form a heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents, wherein the heterocyclyl may also be bridged (forming a bicyclic moiety with a methylene, ethylene or propylene bridge), provided that 1) when Y<sup>b</sup> is N, then m is not 0 if Y<sup>a</sup> is bound to the ring comprising Y, via a N, S or O in Y<sup>a</sup>, or 2) when m and n are both 0 then Y<sup>b</sup> is -CH-.

50. The compound according to claim 49, wherein X is optionally substituted with one, two or three substituents independently selected from the group consisting of halo, oxo, hydroxy, C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl, methoxy, HalCH<sub>2</sub>-O-, Hal<sub>2</sub>CH-O-, Hal<sub>3</sub>C-O- (preferably F<sub>3</sub>C-O-), NH<sub>2</sub>-, -N(C<sub>1</sub>-C<sub>3</sub>alkyl)<sub>2</sub>, -CN, -S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>4</sub>alkyl, -CF<sub>3</sub>, and mono-, di-, or tri- halo substituted alkyl, or, when there are two optional substituents bonded to adjacent atoms of the phenyl, thienyl, or pyridyl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heteroalkyl having 1, 2, or 3 annular heteroatoms.
51. The compound according to claim 49, wherein X is selected from the group consisting of phenyl, pyridyl, thienyl and furyl, each of which is optionally substituted with one, two or three independently selected substituents.
52. The compound according to claim 49, wherein X is selected from the group consisting of phenyl, pyridyl, thienyl and furyl, each of which is optionally substituted with one, two or three substituents independently selected from the group consisting of halo, oxo, hydroxy, C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl, methoxy, HalCH<sub>2</sub>-O-, Hal<sub>2</sub>CH-O-, Hal<sub>3</sub>C-O- (preferably F<sub>3</sub>C-O-), NH<sub>2</sub>-, -N(C<sub>1</sub>-C<sub>3</sub>alkyl)<sub>2</sub>, -CN, -S(O)<sub>0-2</sub>-C<sub>1</sub>-C<sub>4</sub>alkyl, -CF<sub>3</sub>, and mono-, di-, or tri- halo substituted alkyl, or, when there are two optional substituents bonded to adjacent

atoms of the phenyl, thienyl, or pyridyl they, together with the atoms to which they are bonded, optionally form a 5- or 6- membered cycloalkyl or heteroalkyl having 1, 2, or 3 annular heteroatoms.

53. The compound according to claim 49, wherein Ar is optionally substituted with one or two substituents independently selected from the group consisting of halo, nitro, hydroxy, C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl, methoxy, HalCH<sub>2</sub>-O-, Hal<sub>2</sub>CH-O-, Hal<sub>3</sub>C-O- (preferably F<sub>3</sub>C-O-), and mono-, di-, or tri- halo substituted alkyl.
54. The compound according to claim 49, wherein Ar is selected from the group consisting of phenyl, pyridyl, pyrimidyl, benzofuryl, benzothienyl, thienyl and furanyl, each of which is optionally substituted with one or two substituents.
55. The compound according to claim 49, wherein Ar is selected from the group consisting of phenyl, pyridyl, pyrimidyl, benzofuryl, benzothienyl, thienyl and furanyl, each of which is optionally substituted with one or two substituents independently selected from the group consisting of halo, nitro, hydroxy, C<sub>1</sub>-C<sub>3</sub>-hydrocarbyl, methoxy, HalCH<sub>2</sub>-O-, Hal<sub>2</sub>CH-O-, Hal<sub>3</sub>C-O- (preferably F<sub>3</sub>C-O-), and mono-, di-, or tri- halo substituted alkyl.
56. The compound according to claim 49, wherein X<sup>a</sup> comprises a moiety selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycyl, each of which is optionally substituted with from 1 to 3 independently selected substituents.
57. The compound according to claim 49, wherein X<sup>a</sup> comprises a moiety selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycyl, each of which is optionally substituted with from 1 to 3 substituents independently selected from the group consisting of -OH, -NH<sub>2</sub>, -O-C<sub>0</sub>-C<sub>3</sub>alkylCH<sub>3</sub>, halo, oxo, -C(O)NH<sub>2</sub>, -NHC(O)CH<sub>3</sub>.
58. The compound according to claim 49, wherein X<sup>a</sup>-Y<sup>a</sup>- is selected from the group consisting of CH<sub>3</sub>-SO<sub>2</sub>-, CF<sub>3</sub>-C(O)-NH-, CH<sub>3</sub>-C(O)-NH-, ((CH<sub>3</sub>)<sub>2</sub>N)<sub>2</sub>-C=N-, (CH<sub>3</sub>)<sub>2</sub>N-, CH<sub>3</sub>-O-CH<sub>2</sub>-C(O)-NH-, (CH<sub>3</sub>)<sub>2</sub>N-CH<sub>2</sub>-C(O)-NH-, CH<sub>3</sub>CH<sub>2</sub>-N(CH<sub>3</sub>)-, CF<sub>3</sub>CH<sub>2</sub>-NH-, H-, HO-, CH<sub>3</sub>-O-C(O)-NH-, H<sub>2</sub>N-, CH<sub>3</sub>CH<sub>2</sub>-NH-, H<sub>2</sub>N-C(O)-, phenyl-CH<sub>2</sub>-O-C(O)-N(CH<sub>2</sub>CH<sub>3</sub>)-, CH<sub>3</sub>CH<sub>2</sub>-NH-, F, CH<sub>3</sub>-O-CH<sub>2</sub>-C(O)-NH-, heterocyclyl-heterocyclyl, heterocyclyl-heteroaryl, aryl-NH-, heteroaryl-NH-, (CH<sub>3</sub>)<sub>2</sub>N-CH<sub>2</sub>-C(O)-NH- and HO-CH<sub>2</sub>CH<sub>2</sub>-NH-.

59. The compound according to claim 49, wherein the compounds are represented by a formula selected from the group consisting of:



# INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/066045

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D207/32 C07D213/40 C07D213/56 C07D213/61 C07D295/14  
C07D307/52 C07D317/58 C07D333/28 C07D333/36 C07D333/38  
C07D401/12 C07D409/12 C07D409/14 C07D413/12 C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K C07C A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/030705 A1 (METHYLGENE INC [CA]; MORADEI OSCAR [CA]; PAQUIN ISABELLE [CA]; LEIT SI) 7 April 2005 (2005-04-07) cited in the application the whole document	1-59
X	US 3 576 869 A (SCHELLENBAUM MAX ET AL) 27 April 1971 (1971-04-27) compounds 11,13,29	13,24
X	CHARLES ET AL.: "Synthesis of substituted Benzamides, Benzimidazoles and Benzoxazines as potential Anthelmintic and Antimicrobial Agents" ARCHIV DER PHARMAZIE, vol. 315, no. 2, 1982, pages 97-103, XP002439189 compound 10	16-22,45
	-/--	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 June 2007

Date of mailing of the international search report

05/07/2007

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Fritz, Martin



# INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/066045

G(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X,P	WO 2006/122319 A (TAKEDA SAN DIEGO INC [US]; BRESSI JEROME C [US]; BROWN JASON W [US]; G) 16 November 2006 (2006-11-16) p. 106, 5th - 8th structural formula p. 107, 1st, 2nd structural formula -----	1,4,6,9, 13,16

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Information on patent family members

International application No

PCT/US2007/066045

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WO 2006122319 A	16-11-2006	NONE	